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MYASTHENIA GRAVIS ASSOCIATED WITH ADRENOCORTICAL INSUFFICIENCY*

Report of a Case with Post-Mortem Findings and a Review of the Literature

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SINCE 1901, when Laquer and Weigert[1] first demonstrated a tumor of the thymus in a patient with myasthenia gravis, there have been many attempts to establish an endocrine basis for the myasthenic syndrome. In a comprehensive review published in 1943, McEachern[2] summarizes with the statement that "myasthenia gravis does not appear to be connected with endocrine dysfunction except during pregnancy or in relation to the menses or to thyroid activity." After evaluation of the available clinical and experimental data, he could find no conclusive proof of an endocrine function for the thymus, but suggested that the gland might produce a hypothetical "curariform-agent." Recent experimental work of Torda and Wolff[3] has indicated that ether extracts of thymus have a definitely depressive effect on acetylcholine synthesis and thus may influence the development of the myasthenic syndrome.

Unfortunately, many of the earlier clinical observations on this subject are difficult to interpret because a satisfactory clinical test for myasthenia gravis has been available only since 1935 with the introduction of Neostigmine (Prostigmine) by Walker[4] and Viets and Schwab.[5] Except for a few entirely speculative discussions[6, 7] and isolated case reports[8, 9] of myasthenic patients treated empirically (and unsuccessfully) with extracts of the adrenal glands, there is nothing in the medical literature of the past two decades — that is, to 1948 — linking myasthenia gravis with adrenocortical insufficiency on a firm basis.[10]

In 1948 Soffer et al.[11] reported on the use of pituitary adrenocorticotrophic hormone (ACTH) in a young female with moderately severe myasthenia gravis of one year's duration and radiologic evidence of an enlarged thymus. In addition to the striking metabolic changes that occurred, a remarkable symptomatic improvement began three days after the conclusion of therapy so that within a month, the patient had reduced her Prostigmine intake to zero (from 210 to 300 mg. daily). The authors suggest that the beneficial action of the hormone was probably due to a "dissolution of thymic lymphocytes" in the presence of intact adrenal glands. Thus, they found that similar, although less striking results followed the administration of 5 cc. of adrenocortical extract three times a day for four days.

Similar results in a series of 17 patients with myasthenia gravis have been reported by Torda and Wolff.[12] Partial symptomatic remissions lasting up to three months occurred in 11 of these cases. Clinical improvement was accompanied by enhanced ability of the blood serum to support acetylcholine synthesis; better performance on ergographic testing; and restoration of the electromyogram to normal.

These investigators believe that the beneficial effect of ACTH in this disease is related to its demonstrated ability to increase acetycholine synthesis in vivo, as well as its property of inducing shrinkage of the thymus and other lymphatic tissue.

Although many mild cases of myasthenia gravis are seen and treated successfully on an ambulatory basis, the more severe forms are rarely seen in most hospitals. In the past fifteen years at this institution, for example, there have been only 12 proved cases in some 300,000 general admissions (1:25,000), in which 5 patients died and 2 came to post-mortem examination, with the finding of a large thymoma in 1 of these.[13]

Adrenocortical insufficiency (Addison's disease) appears, contrary to the usual opinion, to be almost equally rare, having been responsible for only 0.4 deaths per 100,000 in the United States Registration Area in 1930, according to Guttman.[14]

The case reported below is presented because of unmistakable clinical and post-mortem evidence of myasthenia gravis with an associated adrenocortical insufficiency. Post-mortem examination also revealed an enlarged thymus, which, despite careful roentgenologic studies, was not apparent during life. In addition to the rarity of this triad, it is believed that it may be of interest to consider some

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of the manifold theoretical aspects of this unusual experiment of nature.

Case Report

S.T. (L.H. 264-908), an 18-year-old native-born high-school student of Italian-American extraction, was admitted to the hospital on July 23, 1947 complaining of severe, generalized weakness of about 1 year's duration. Approximately 3 months before admission he began to complain at intervals of "double vision," and shortly thereafter it was noted that the right upper eyelid "drooped." One week later, ptosis of the left eyelid appeared, but the patient noted no diminution in visual acuity with these disabilities. In the 2 months prior to admission he had had intermittent episodes of slurring of speech, difficulty in chewing and swallowing and occasional regurgitation of liquids through the nose. Four weeks prior to admission he began to lose his appetite, and generalized weakness, nausea, vomiting and severe constipation, requiring an enema "every 2 or 3 days," developed. In the week prior to admission, he had been able to retain only liquids. His mother estimated that he had lost about 20 pounds in the preceding 12 months.

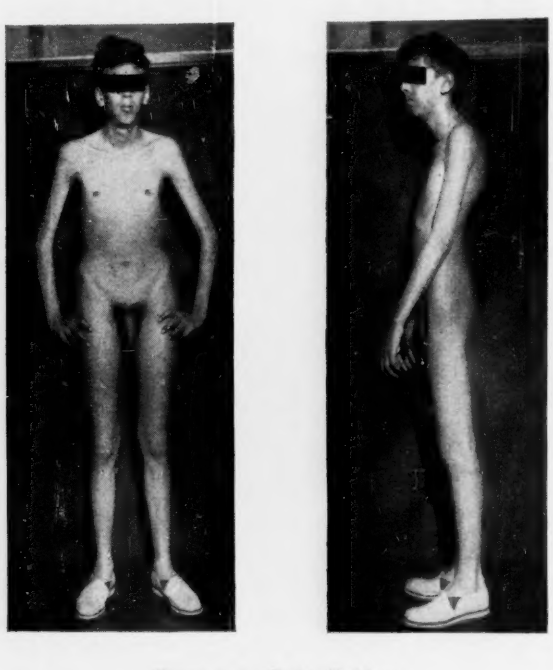

Figure 1. *Body Habitus.*
Note the eunuchoid physique, but normal external genitalia.

The patient had had measles, mumps and pertussis in infancy, without complications. There was no family history of endocrine or neurologic disease or of exposure to tuberculosis.

Physical examination revealed a tall, asthenic, undernourished youth (Fig. 1) with apathetic facies, open mouth, drooping eyelids and nasal twang to his voice. Although he was able to answer questions intelligently, his speech was slurred at intervals; he was slow in comprehension, and tired very easily. He appeared chronically ill, but seemed to be in no acute distress, respiratory or otherwise. Body measurements were as follows: height, 176 cm. (span, 180 cm.), and weight, 51.2 kg. There was "bronzing" of the skin, most marked in the lumbodorsal region. Numerous pigmented nevi (brownish and nonhairy), measuring 1 or 2 mm. in diameter, were distributed over the entire body. Hair distribution was normal. There was suggestive pallor of the mucous membranes. Both eyeballs were somewhat protuberant. Tension was normal. The right pupil was slightly larger than the left, but both reacted promptly to light. The optic disks and fundi were within normal limits. Moderate dorsal kyphosis was noted. The thyroid gland was slightly enlarged, without nodules or bruit. There was poor expansion of the thoracic cage, but no widening of the superior mediastinum by percussion. The chest was slightly hyperresonant but otherwise clear to percussion and auscultation. The heart was not enlarged. There was a Grade II soft, blowing, apical systolic murmur heard best in sitting position, but not transmitted. Examination of the abdomen revealed no palpable organs, masses, hernias or tenderness. The pubic hair was of normal male distribution, with a normal adolescent penis; both testes were in the scrotum.

Neurologic examination showed the patient to be left-handed. Gait and station were not tested because of debility (they were subsequently found to be normal). There was marked bilateral ptosis, with virtually complete bilateral external ophthalmoplegia and bilateral masseter weakness. The facies was myopathic with overactivity of the corrugator-frontalis musculature. There was a diminished gag reflex. Swallowing was difficult. The patient was barely able to shrug the shoulders against resistance. The tongue protruded in the midline, without tremor, atrophy or fasciculations. On motor examination the muscles were hypotonic throughout. He could hardly register any force on the hand dynamometer ("normal range," 100 to 200). He was unable to sit up unaided, to hold the arms extended or to hold the legs above horizontal, and yet no obvious atrophy, pseudohypertrophy or fasciculations were present. In general, the proximal musculature was more severely involved than the distal; there was no obvious involvement of the intercostal, diaphragm or abdominal rectus muscles. Easy fatigue was noted on execution of rapid motions throughout. All deep tendon and superficial reflexes were present and equal bilaterally, but hypoactive. No abnormal reflexes were observed. Sensory examination and tests of co-ordination were negative.

Table 1. *Significant Clinical, Hematologic and Chemical Determinations.*

Date	Body Weight	Eye Signs	Dynamometer Readings	Blood Pressure	Red-Cell Count	Hemoglobin	Hematocrit	Total Protein
1947	*kg.*		*left hand*		*x10⁶*	*gm./100 cc.*	*%*	*gm./100 cc.*
7/23*	51.2	+++	30	76/60	5.2	14.5	42	6.0
8/1–9/13†	51.6	+	80	110/70	2.9	8.1	24	5.3
9/10‡	51.2	+	70	70/50	4.1	12.6	42	—
9/18§	51.0	+	80	94/70	4.0	13.0	35	—
11/23¶	—	+	—	126/100	4.1	14.4	45	8.0

*On admission.
†After treatment.
‡After withdrawal of Neostigmine (average daily sodium intake and excretion: 4 and 17 gm., respectively).
§At discharge.
¶On final admission.

The temperature was 99.3°F., the pulse 92, with a regular sinus rhythm, and the respirations 16. The blood pressure was 76/60 in the right arm and 68/52 in the left.

Repeated urinalyses were negative, as was the 24-hour test for melanin. A serologic test for syphilis was negative. The blood urea nitrogen was 45 mg. per 100 cc. on admission (range, 14 to 45 mg.), the blood sugar 69 mg. per 100 cc. (range, 43 to 111 mg.), and the total protein 6.0 gm. per 100 cc. on admission (range, 5.3 to 6.0 gm. with from 3.2 to 3.8 gm. of albumin and 2.1 to 2.6 gm. of globulin). The serum chloride was 88 milliequiv. per liter (range, 88 to 114 milliequiv.), the carbon dioxide combining power 47 vol. per cent (range, 37 to 76 vol. per cent), the serum sodium 128.7 to 142.4 milliequiv. per liter, and the serum potassium 6.7 milliequiv. per liter on admission (range, 6.0 to 8.4 milliequiv.). Examination of the blood showed a red-cell count of 5,200,000, with a hemoglobin of 14.5 gm. per 100 cc., and a white-cell count of 14,200, with 60 per cent neutrophils and 35 per cent lymphocytes. The hematocrit was 42 per cent. Subsequently, on hydration, the hematocrit fell to 22 per cent, the hemoglobin to 8.1 gm. per 100 cc., and the red-cell count to 2,900,000. The urea clearance, which was 39 and 33 per cent of normal on admission rose to 76 and 79 per cent of normal after treatment. Lumbar puncture disclosed a clear, colorless fluid containing no cells and with normal dynamics, a protein of 20 mg. and a chloride of 702 mg. per 100 cc. and negative mastic and Wassermann tests. The basal metabolism rate was −26 to −20 per cent. The serum cholesterol was 110 mg. per 100 cc. An intravenous glucose tolerance test (52.5 gm. administered intravenously in 1 hour) was as follows: fasting, 70 mg., at 1 hour 303 mg., at 2 hours 102 mg., at 3 hours 62 mg., and at 4 hours 66 mg. per 100 cc. Twenty-four-hour excretions (after 30 days on a high-protein diet) were 0.040 gm. of creatine and 0.806 gm. of creatinine. An electrocardiogram showed right-axis deviation, prolonged PR and QT intervals and flattening of the T waves. The Robinson-Powers-Kepler[15, 16] "water" test, Parts I and II, was positive. Thorn's adrenocorticotrophic hormone test[17] was positive — that is, there was no response. A 17-ketosteroid assay disclosed less than 1 mg. in 24 hours (gonadotropin assay was less than 4 mouse units in 24 hours). The tuberculin test (first-strength purefied protein derivative) was negative. Sternal-marrow puncture was interpreted as demonstrating "somewhat hypoplastic marrow with a high percentage of mononuclear cells." An electroencephalogram revealed generalized dysrhythmia, especially marked in the occipital areas. X-ray films of the skull were within normal limits. The chest showed no thymic enlargement; the heart was vertical in position, and the lung fields disclosed increased markings suggestive of pulmonary fibrosis. The abdomen demonstrated no calcification in the region of the adrenal glands. A gastrointestinal series was normal. The bones of the hands were consistent with a normal bone age (18 years, 9 months, by Todd's standards). The Viets-Schwab[18] diagnostic exclusion test for myasthenia gravis gave no response to 0.0015 gm. of Neostigmine methylsulfate (H) on the first test (??) but gave *markedly positive* responses to all subsequent efforts.

During the first 2 weeks in the hospital, it became apparent that the signs and symptoms were suggestive of myasthenia gravis in association with evidence of adrenocortical insufficiency. Appropriate diagnostic studies, the results of which are outlined below, confirmed both clinical impressions, and therapy for each was promptly instituted.

After the administration of 35 cc. of aqueous adrenocortical extract intravenously, 10 mg. of desoxycorticosterone acetate intramuscularly and 3000 cc. of 5 per cent dextrose in physiologic saline solution intravenously, the serum electrolytes, blood sugar and general clinical state were restored to within normal limits (except for persistent ptosis, ophthalmoplegia and muscular weakness) in the first 36 hours after admission. However, a latent anemia of normocytic type became evident after hydration, and a persistent tendency to hypoglycemia and hypometabolism (Table 1) still had to be dealt with. Accordingly, a high-protein diet with frequent feedings was started, and ferrous sulfate (0.32 gm. three times a day) and eventually three small (250-cc.) blood transfusions were given. Meanwhile, to help the patient chew his food, three doses of Neostigmine methylsulfate (0.001 gm. each) were given shortly before each meal.

As soon as it was established that relatively normal serum electrolyte values could be maintained by the use of 5 mg. of desoxycorticosterone every two days, an attempt was made to determine the basic (oral) requirements for Neostigmine. This eventually turned out to be 30 mg. of the bromide given three times daily about 20 minutes before meals in addition to an equal amount at 3:00 and 8:00 p.m. (total dose 10 tablets or 150 mg. daily). The patient tolerated these large doses of the drug without requiring atropine or belladonna, the "eye signs" improved dramatically, and he gradually became ambulatory and was able to register three or four times the force on the dynamometer that had been possible on admission. Omission of the Neostigmine resulted in a prompt "myasthenic relapse" with no obvious effect on the blood pressure, fasting blood sugar or serum electrolytes.

By the end of the 6th week, maximal benefit from the various replacement therapies was attained, and after careful consideration it was decided that a trial period of withdrawal of all salt and desoxycorticosterone was justified prior to the implantation of pellets. Accordingly, while the optimal daily intake of Neostigmine and ephedrine was maintained and the diet continued, the added sodium chloride and desoxycorticosterone were discontinued. Symptoms of impending adrenal crisis were first noted after 8 days (Table 1) with the development of nausea, anorexia, apathy and a fall in blood pressure to 70/50. Significant alterations in hematocrit, serum electrolytes and excretion of urinary chloride during this period, are summarized in Table 1. The patient responded promptly to the use of adrenocortical extract, desoxycorticosterone and parenteral administration of fluids.

Soon after he was stabilized again (9th week), four pellets of desoxycorticosterone acetate (weighing 75 mg. each) were implanted in the loose areolar tissue of the interscapular area, and he was discharged. At that time he was up and about the ward, had no complaints and was beginning to develop a voracious appetite. There were no signs of toxicity

TABLE 1 (*Concluded*).

DATE	SERUM ALBUMIN	SERUM GLOBULIN	BLOOD UREA NITROGEN	FASTING BLOOD SUGAR	CARBON DIOXIDE COMBINING POWER	SERUM CHLORIDE	SERUM SODIUM	SERUM POTASSIUM
1947	*gm./100 cc.*	*gm./100 cc.*	*mg./100 cc.*	*mg./100 cc.*	*vol. per cent*	*milliequiv./liter*	*milliequiv./liter*	*milliequiv./liter*
7/23*	3.8	2.2	45	69	47.0	88.0	128.7	6.7
8/1–9/13†	3.0	2.3	15	111	76.0	103.0	139.4	6.5
9/10‡	—	—	28	63	38.0	93.0	131.2	7.1
9/18§	—	—	24	73	62.0	107.0	133.9	—
11/23¶	5.4	2.6	29	70	65.9	98.8	142.4	8.4

from desoxycorticosterone; the weight was 51.0 kg., and the blood pressure 94/70. He was instructed to avoid overexertion, stay as free of infections as possible and to continue with the high-protein diet, ferrous sulfate, ephedrine, and Neostigmine as outlined above. No extra salt was recommended, nor was the potassium (dietary) restricted. The entire hospital course had been afebrile and without obvious complicating infections of any type.

In the 9 weeks after discharge on September 17, the patient was seen on three occasions. He was taking his medication regularly, felt well and had had no unusual symptoms.

On November 22 he was seen in the Emergency Ward, complaining of "asthma." The blood pressure was found to be

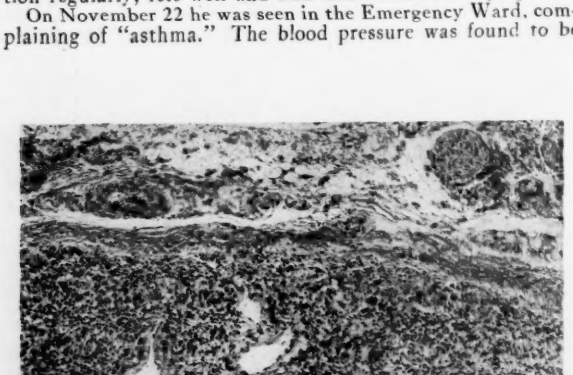

FIGURE 2. *Photomicrograph of the Left Adrenal Gland (Hematoxylin and Eosin Stain x56).*
Note the absence of clear-cut demarcation between the cortex and medulla.

100/60, and the temperature was 98.2°F.; the respirations were 24 per minute and labored, with a few high-pitched, sibilant rales at the right lung base. He was given aminophylline with some relief and was sent home with instructions to return to the Medical Out-Patient Department.

Twelve hours later he was readmitted to the hospital, complaining of progressive dyspnea and a "tight feeling" in the upper anterior portion of the chest. Physical examination revealed an acutely ill, severely dyspneic, cyanotic and apprehensive youth, sitting bolt upright in bed, using all his accessory muscles of respiration and yet with little expansion of the thoracic cage. The skin was cool and dry, and a striking increase in bronze pigmentation had occurred. Sibilant rhonchi and diminished breath sounds were present throughout all lung fields. The heart size seemed unchanged clinically, and the apical systolic murmur previously heard was also unchanged. The remainder of the physical examination, including the neurologic findings, was unchanged. There was severe generalized asthenia, slight ptosis and some external ophthalmoplegia. There was no evidence of tracheal displacement, hepatomegaly, cervical venous distention or peripheral edema.

The temperature was 99.9°F., the pulse 72 (with a regular sinus rhythm), and the respirations 30; the blood pressure was 126/100 (checked).

Urinalysis was negative except for a ++ test for acetone. Examination of the blood disclosed a red-cell count of 4,100,000, with a hemoglobin of 14.4 gm., and a white-cell count of 12,200, with 62 per cent neutrophils, 22 per cent lymphocytes, 11 per cent monocytes and 4 per cent eosinophils. The sedimentation rate (corrected) was 8 mm. per hour. The hematocrit was 45 per cent. The fasting blood sugar was 70 mg. the blood urea nitrogen 29 mg., and the total protein 8.0 gm. per 100 cc., with 5.4 gm. of albumin and 2.6 gm. of globulin; the chloride was 98.8 and 102.6 milliequiv. per liter on two determinations, and the carbon dioxide combining power was 65.9 and 68.6 vol. per cent. The serum calcium was 11.6 mg. per 100 cc., and the serum sodium 142.4 milliequiv. and the serum potassium 8.4 milliequiv. per liter. The venous pressure was equivalent to 110 mm. of saline solution.

An x-ray film of the chest was interpreted as showing "Enlargement of 2.5 cm. in cardiac size since the last previous examination (8 weeks); increased pulmonary markings throughout; and no evidence of a mass in the superior mediastinum." An electrocardiogram revealed a wandering pacemaker, occasional nodal premature beats, right-axis deviation and inverted T waves in Leads V_2 and V_4.

The patient was immediately placed in an oxygen tent and later was given a helium-oxygen mixture by mask, with transitory relief. Small doses of epinephrine and aminophylline intravenously failed to help the dyspnea, which was both inspiratory and expiratory in type. Parenteral administration of Neostigmine (0.001 gm. every 4 hours) and atropine (0.0006 gm. with each dose of Neostigmine) was begun. A constant subcutaneous infusion of dextrose in saline solution was started, and he was given 8.0 cc. of adrenocortical extract intramuscularly.

Because there was some evidence (cardiac enlargement on x-ray study, T-wave changes in the electrocardiogram and relative diastolic hypertension) of acute or incipient cardiac decompensation due to an overdose of desoxycorticosterone, two of the four pellets were removed, and the patient was given 4 cc. of lanatoside C (Cedilanid) intravenously; a fresh solution of 0.5 per cent potassium chloride was prepared for intravenous use, but before it could be given, a series of tetanic convulsions (not relieved by 10 cc. of calcium gluconate intravenously) occurred, marked dyspnea, cyanosis and peripheral vascular collapse developed, and the patient finally died some 13 hours after admission. Respirations ceased a minute or more before cardiac standstill.

At autopsy,* performed 10 hours after death, sections of skin demonstrated a typical pigmented nevus and hyperpigmentation of the malpighian layer of the epidermis. Grossly, the lungs showed chronic fibrous pleuritis, with a subpleural hemorrhage, in both upper lobes; intra-alveolar hemorrhage, marked, in both lower lobes; slight pulmonary edema and slight acute and chronic bronchitis of all lobes. There was no evidence of pulmonary tuberculosis.

Microscopically, there was simple atrophy of the myocardium, with moderate fatty infiltration of the right ventricle and a healed, nondeforming endocarditis.

The right adrenal gland weighed 2.5 and the left (Fig. 2) 9.5 gm. Both were soft, friable and brownish. On histologic examination there was no clearcut demarcation between cortex and medulla, apparently owing to atrophy rather than aplasia, since there were large entering veins. There was no histologic evidence of tuberculosis.

The axial and appendicular musculature appeared normal grossly. On microscopical examination, one focus of lymphocytic infiltration was found in the psoas muscle, whereas sections from the rectus abdominis, deltoid and pectoral muscles were all normal.

Examination of the remaining endocrine system revealed the thyroid gland, which weighed 15 gm., to be normal grossly, with histologic evidence of lymphoid hyperplasia and a moderate increase in colloid. The pituitary body weighed 1 gm., was reddish-brown and disclosed a striking increase in cells, which showed basophilic staining with hematoxylin and eosin. These cells were smaller than the usual basophil size. No normal-appearing basophil cells were seen. A few large pale-staining cells (chromophobe?) with foamy cytoplasm and a few eosinophilic cells were seen. Only a few cells stained deep red with azan — that is, they were mostly chromophobe in type. Histologic examination of the testes showed slight interstitial fibrosis, with only slight evidence of spermatogenesis. The prostate gland was within normal limits, grossly and microscopically.

The thymus weighed 45 gm., was flattened and hyperemic and was considered to be moderately involuted. There was

*Performed by Richard W. Watts, M.D.

no evidence grossly of tracheal obstruction. Tissue sections (Fig. 3) showed a thin, irregular cortex, with a well marked medulla. The cortex consisted of closely packed, small, round cells. Hassall's corpuscles were numerous and ranged in appearance from a focus of large cells with round or oval, pale basophilic nuclei and eosinophilic cytoplasm to a homogeneous, acellular, eosinophilic mass.

The brain weighed 1670 gm. There was moderate venous dilatation over both convexities. After 7 days' fixation, the cortex appeared darker brown and the white matter less firm than usual. Except for evidence of hyperemia of the superficial layers of the cerebral cortex, the microscopical sections of the cerebral hemispheres, brain stem, basal ganglions, cerebellum and spinal cord were not remarkable.

Discussion

In view of the clinical syndrome presented together with the laboratory findings of fasting hypoglycemia, mild azotemia, low serum sodium and positive responses to the "water" and adrenocorticotrophic hormone tests, we have accepted the simultaneous diagnoses of Addison's disease and myasthenia gravis in this patient. As pointed out below, no major objections to this conclusion were revealed by autopsy since the degree of enlargement of the thymus is compatible with either condition.[2]

The development of "eye signs," slurred speech and dysphagia one month before the onset of symptoms clearly attributable to adrenal insufficiency may be interpreted as indicating that the myasthenic syndrome was primary in this patient. However, the initial onset with weakness makes it difficult to decide this point, and we believe that, in all probability, the two pathologic processes were essentially simultaneous in onset.

In view of the demonstration by Torda and Wolff[19] that hypophysectomy in rats induces changes in the electromyogram that closely resemble those noted in patients with myasthenia gravis, the pituitary changes in this case are worth commenting on. Histologically, the gland revealed hyperplasia of chromophobe cells with few acidophils and almost no basophils, a change quite similar to that described by Crooke and Russell[20] in cases of Addison's disease. The peculiar eosinophilic colloid material observed in the pituitary gland of several patients who have died of myasthenia gravis[19] was not found. We do not believe, therefore, that the available evidence in this case suggests a "pluriglandular disorder," although this point is debatable.

As stated above, there seems to be no conclusive evidence that these two pathologic processes are related. Brem and Wechsler[21] suggest that there may be such a relation in their report of extensive vacuolar degeneration in the adrenal glands, which "in some areas had gone on to complete necrosis," in 2 cases of myasthenia gravis that came to postmortem examination.

Finally, the nature and cause of the patient's sudden death presented a perplexing problem because of the multiplicity of possible contributing factors. Experience has shown that myasthenic patients tolerate undue stress, shock, injuries, infections or overexertion poorly.[2] Death is usually due to paralysis of respiratory muscles or exhaustion of medullary centers, or follows laryngospasm.[2, 10] As Selye[22] and others have emphasized, patients with Addison's disease react adversely or inadequately to the same environmental factors as those listed above for myasthenic patients. A brief review of the endocrine literature on this subject indicates that death in adrenal insufficiency may take many forms, most commonly a fatal hypoglycemia.[23] However, several cases have terminated without any demonstrable alteration of blood constituents.[24]

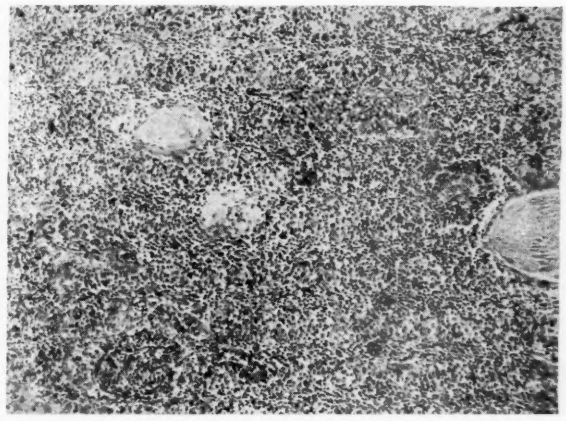

Figure 3. *Photomicrograph of the Thymus, Showing Closely Packed Round Cells in the Medulla (Hematoxylin and Eosin Stain x82).*

In summary, no single mechanism for death can reasonably be suggested that is compatible with all or most of the clinical, laboratory and postmortem findings in this unusual case.

Summary

A fatal case of myasthenia gravis in a young, adolescent male, complicated by a severe adrenocortical insufficiency, is reported.

Post-mortem examination revealed an enlarged thymus gland, one focus of lymphocytic infiltration in the psoas muscle, extensive atrophy of the cortexes of both adrenal glands and unusual, probably nonspecific changes in the pituitary gland.

This situation, believed to be unique in the available medical literature, is considered to be simply an uncommon coincidence of two pathologic states, each relatively rare in its own right.

We are indebted to Dr. Wade Price for his detailed chemical studies in this case, to Drs. Max Miller and Reginald Shipley for aid in the management of the patient, to Dr. H. Z. Lund for furnishing the photomicrographs and to Dr. George Perera for advice in the preparation of the manuscript.

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MARCH HEMOGLOBINURIA IN A WOMAN*

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THE literature now contains many reports of cases of "march hemoglobinuria" in men,[1-18] but to date there has been only one report of this condition occurring in a woman.[14] The diagnosis of march hemoglobinuria is made in subjects in whom marching, walking or running occasions the passage of red urine containing hemoglobin in solution.[1-18]

We have recently had the opportunity of studying a case of march hemoglobinuria in a young woman in whom attacks were precipitated by short walks. The present communication describes the clinical and laboratory investigations made in this case.

Case Report

A. G., a single 30-year-old woman, a physicist, visited her physician§ in April, 1948, complaining of having voided red urine on many occasions during the past 3 months. The patient had a noncontributory family history and a past history of typhoid fever in childhood. In December, 1947, she had had an undiagnosed respiratory infection with symptoms similar to those of an illness diagnosed as "grippe" prevalent in the locality at that time and from which she recovered in approximately 2 weeks. Early in February she first noticed the frequent passage of Burgundy-red or brown urine after she had walked a distance of approximately ½ mile in 10 minutes. Mild, poorly localized abdominal cramps occurred during the course of some of the walks, which were followed by the voiding of discolored urine. She also reported that during this interval similar walks at times had no such effect and that walks of 1 mile at the somewhat slower rate of 2½ miles per hour were not followed by the passage of red urine. In June and July she noted that ½-mile walks were not followed by the passage of red urine whereas walks of 1⅛ miles at approximately 3½ miles an hour might or might not give rise to abnormal pigmentation of the urine. She also observed that roller skating 3 miles in 35 minutes and bicycling up to 10¼ miles in 85 minutes were not followed by discoloration of the urine.

Physical examination disclosed a well developed and well nourished, somewhat sallow-complexioned young woman with no apparent physical abnormalities; posture was normal. Roentgenographic examination of the abdomen showed the kidneys to be normal in position and appearance; the liver and spleen were not enlarged. Several examinations of specimens of urine obtained before the patient walked revealed nothing of note except for occasional leukocytes in the sediment; the blood nonprotein nitrogen and serum bilirubin concentrations and the icteric index were normal. The hemoglobin level in June was 12.4 gm. per 100 cc., and the red-cell count was 3,790,000; the reticulocyte percentage was 0.6. Blood smears showed no spherocytes or target cells; no sickling tendency was found. The platelets numbered 174,000, and the white-cell count was 6200. The corrected sedimentation index was 0.21 mm. per minute. The blood was Group O and Rh+.

Physiologic studies were completed in August; hemoglobinuria persisted in variable degree thereafter for approximately 1 year.

Methods of Investigation

The methods of investigation used in this study were the same as those in previous studies of hemoglobinuria reported from these laboratories,[1, 19, 20] with the following additions or changes. The osmotic fragility of the erythrocytes was measured according to the method of Shen, Ham and Fleming,[21] and the mechanical fragility of the erythrocytes by the method of Shen, Castle and Fleming.[22] Weak and incomplete Rh agglutinins were sought by the method of Coombs, Mourant and Race[23]¶ and cold hemagglutinins by the method used by

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§Dr. Herbert Saver, of Boston, recognized the symptoms of march hemoglobinuria when he found a pigmented urine to contain no erythrocytes but much hemoglobin by the benzidine test; he kindly referred the patient to us for study.

¶The fragility tests and the Coombs test were performed by Miss Eleanor M. Fleming, of the Thorndike Memorial Laboratory, Boston City Hospital.

Finland et al.[24] The concentrations of hemoglobin in the plasma and urine were measured by the benzidine method of Bing and Baker,[25, 26] using purified benzidine[26] and the Evelyn photoelectric colorimeter at a wave length of 660 microns, the results being calculated from data obtained on solutions of known hemoglobin concentrations.

Results

Studies were made in this subject before, during, and for varying lengths of time after five walks of from 1 to 15 miles (Table 1). Sodium bicarbonate was administered in sufficient amount to keep the urine alkaline during the 15-mile walk.[1] The plasma and urine contained red pigment after each of these walks. Poorly localized and moderately severe abdominal cramps not accompanied by abdominal tenderness or spasm occurred during and for a brief period after the 15-mile walk.

The blood Wassermann test was negative. The Donath–Landsteiner test for paroxysmal hemoglobinuria of the chill (syphilitic) type was also negative. No cold hemagglutinins or weak and incomplete Rh agglutinins were detected. Normal osmotic and mechanical fragilities of the erythrocytes were found in blood samples drawn before and immediately after a walk that gave rise to hemoglobinuria.

The plasma hemoglobin concentration at the end of walks of 1 to 3 miles was between 32 and 64 mg. per 100 cc. (Table 1). Walks that occasioned plasma hemoglobin levels of approximately 50 mg. per 100 cc. or over gave rise to grossly visible hemoglobinuria. The hemoglobin concentration of the plasma returned to normal approximately four hours after the end of these walks (Table 1).

Table 1. *Quantitative Studies of Plasma Hemoglobin and Bilirubin and of Urine Hemoglobin during and after Walks That Produced Hemoglobinuria in Subject A. G.**

Date	Nature of Study	Time	Plasma Findings		Urine Hemoglobin	
			Hemoglobin	Bilirubin	Concentration	Output
1948			*mg./100 cc.*	*mg./100 cc.*	*mg./100 cc.*	*gm.*
6/12	2-mi. walk with studies at end of 1 and 2 mi. and 1 hr. after	Before walk	6	0.42	0	0
		End of 1 mi. in 18 min.	32	—	0.3	0.001
		End of 2 mi. in 36 min.	58	—	101	0.101
		1 hr. after	43	—	39	0.143
6/24	3-mi. walk with studies at end of 2 and 3 mi. and at intervals thereafter	Before walk	—	0.23	0	0
		End of 2 mi. in 31 min.	—	—	1	0.002
		End of 3 mi. in 48 min.	64	—	974	0.078
		1.5 hr. after	35	—	106	0.101
		3 hr. after	17	0.42	0.3	0.002
		4 hr. after	10	0.48	0	0
7/24	2-mi. walk in normal posture with studies at end and at intervals thereafter	Before walk	3	0.36	0	0
		End of 2 mi. in 31 min.	51	—	8	0.003
		1 hr. after	—	—	20	0.056
		2 hr. after	19	0.74	0.1	0.001
		3.5 hr. after	7	0.81	0	0
	2-mi. walk in moderately kyphotic posture with studies at end	Before walk	7	0.81	0	0
		End of 2 mi. in 31 min.	51	—	50	0.009
8/7	15-mi. walk with studies at intervals during walk and 2.1 hr. later	Before walk	6	—	0	0
		End of 3 mi. in 45 min.	—	—	415	0.095
		End of 5 mi. in 83 min.	148	—	1700	0.340
		End of 7 mi. in 131 min.	197	—	592	0.580
		End of 9 mi. in 168 min.	225	—	688	0.564
		End of 11 mi. in 208 min.	244	—	948	0.568
		End of 13 mi. in 244 min.	230	—	3970	0.597
		End of 15 mi. in 282 min.	215	—	3700	0.628
		2.1 hr. after	132	—	2020	0.949

*Hemoglobinemia and hemoglobinuria occurred also after a 1-mile walk under our observation on 11/23/48; quantitative studies of the plasma and urine hemoglobin were not made on this occasion.

The urine immediately after these walks, which caused grossly visible hemoglobinuria (Table 1), always gave a strongly positive nitric acid test for protein. The sediment of the centrifuged urine specimens contained only occasional erythrocytes and small numbers of leukocytes and granular casts; no hemoglobin casts or hemosiderin granules were found in the pigmented urine specimens obtained after walks. By three to four hours after the end of walks of 1 to 3 miles the urine had again become normal.

The effect of posture was investigated by the application of a cast so as to maintain a kyphotic posture during walking; results of studies of the blood

walks (Table 1). Spectrophotometric studies,* employing a Beckmann spectrophotometer, demonstrated the red pigmentation of the plasma and of the urine to be due to hemoglobin. Points of maximum absorption at 542 and 579 millimicrons were found in the plasma and urine obtained during an attack produced by a walk of 2 miles. When the urine was treated with the reducing agent sodium hydrosulfite only one point of maximum absorption was observed, — at 555 millimicrons, — which corresponds with the point of maximum absorption of reduced hemoglobin. Pigment isolated from the urine was found by spectrophotometric analysis to be oxyhemoglobin together with some methemoglobin. The Schumm test[27] revealed no methemalbumin in the pigmented plasma after several walks.

No enlargement of the liver and spleen was detectable on physical examination after these

*These spectrophotometric studies were made by Dr. F. Lee Rodkey, of the Biochemical Department, Harvard Medical School.

and urine made after a walk in which the subject wore the cast were not different from those obtained after a similar walk without the cast (Table 1 and Fig. 1).

Studies at intervals during the walk of 15 miles in four and seven-tenths hours showed the plasma hemoglobin to increase to a maximum of 244 mg. per 100 cc. at the end of 11 miles, and to decrease to 215 mg. per 100 cc. as the walk continued to 15 miles (Table 1, and Fig. 2). Urine specimens voided at 2-mile intervals during this walk were all dark red and contained hemoglobin in solution. The amount of dissolved hemoglobin voided after each 2-mile interval increased during the first 7 miles of walking and remained at a relatively constant level of excretion during the last 8 miles of walking (Table 1 and Fig. 2).

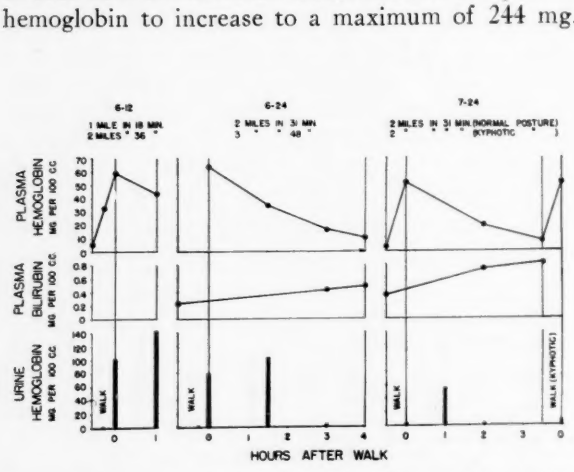
6-12
1 MILE IN 18 MIN.
2 MILES " 36 "
6-24
2 MILES IN 36 MIN.
3 " " 48 "
7-24
2 MILES IN 36 MIN. (NORMAL POSTURE)
2 " " " (KYPHOTIC ")
PLASMA HEMOGLOBIN MG. PER 100 CC.
PLASMA BILIRUBIN MG. PER 100 CC.
URINE HEMOGLOBIN MG. PER 100 CC.
WALK
WALK (KYPHOTIC)
HOURS AFTER WALK

FIGURE 1. *Observations before and after Walks of 1 to 3 Miles (Effect of Kyphotic Posture).*

The whole-blood hemoglobin and the hematocrit values showed no significant changes after walks of 2 or 3 miles; the hematocrit values were 40.5 per cent before and 38.0 per cent immediately after the 15-mile walk.

The total amount of hemoglobin released from the erythrocytes into the plasma in this subject during four walks of 2 or 3 miles was calculated[1] from the data on the hemoglobin concentrations of the plasma and the plasma volume.* Also, the volume of the subject's blood that would be equivalent to these amounts of hemoglobin was estimated[1] from the amount of hemoglobin released in the plasma, calculated as above, and the values for the hemoglobin concentration of the subject's whole blood (Table 2). The calculated total amount of hemoglobin released into the plasma by walks of 2 or 3 miles in four experiments was 1.2 to 1.6 gm. — that is, the hemoglobin equivalent of from 9 to 13 cc. of the subject's blood, or 3.6 to 4.7 cc. of her erythrocytes. Five per cent to approximately 20 per cent of the hemoglobin released into the plasma was excreted in the urine (Table 2).

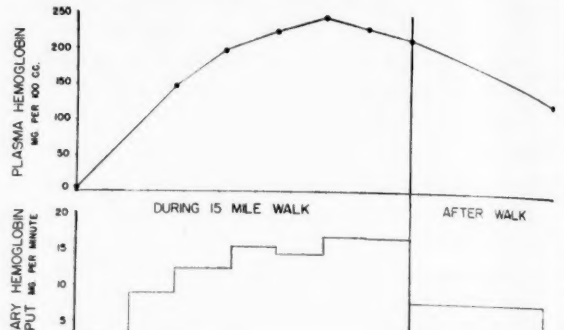

FIGURE 2. *Observations during and after a Walk of 15 Miles.*

The total amount of hemoglobin released intravascularly from the erythrocytes during the prolonged walk of 15 miles taken by this subject was also estimated[19, 20]† to be approximately 10 gm., equivalent to the hemoglobin contained in approximately 80 cc. of the subject's blood or approximately 30 cc. of her erythrocytes.

TABLE 2. *Data after Walks of 2 and 3 Miles.*

Date 1948	Duration of Walk		Plasma Hemoglobin at End of Walk	Hematocrit	Plasma Volume	Hemoglobin Released Into Plasma During Walk	Hemoglobin of Whole Blood	Volume of Blood Equivalent to Hemoglobin Released Into Plasma	Volume of Red Cells Broken During Walk	Total Output of Hemoglobin in Urine	Hemoglobin Released Into Plasma Excreted in Urine
	Miles	Minutes	mg./100 cc.	%	cc.	gm.	gm./100 cc.	cc.	cc.	gm.	%
6/12	2	35	58	36	2500	1.45	12.2	12	4.3	0.25	17
6/24	3	47	64	36	2500	1.60	12.2	13	4.7	0.18	11
7/24 (normal posture)	2	31	51	40	2340	1.19	13.2	9	3.6	0.06	5
7/24 (kyphotic posture)	2	31	51	40	2340	1.19	13.2	9	3.6	—	—

*The plasma volume was estimated from the values for blood volume, calculated on the basis of body surface area, from the chart of Gibson and Evans[28] and the hematocrit values at the end of the exercise.

†Since this walk continued for four and seven-tenths hours the loss of hemoglobin from the plasma by excretion and catabolism after hemolysis had started, as well as the gain to the plasma from continued hemolysis, as the walk progressed, was taken into consideration in these calculations.

Discussion

We have been able to find, to date, reports of 76 cases of the occurrence of hemoglobinuria after physical exertion; only one concerned a female subject. In 56 of these subjects hemoglobinuria was precipitated by walking or marching for a quarter of an hour to several hours[1, 3-12, 14-16]; in 20 athletes hemoglobinuria was observed after strenuous runs.[1, 2, 13, 17] It is now established that entirely healthy athletes frequently exhibit hemoglobinemia and hemoglobinuria after extremely strenuous walks and runs of long duration. Although this intravascular hemolysis occurring after such extreme exertion is considered "physiologic"[2] the development of hemoglobinuria in subjects during short walks or runs constitutes a clinical problem.

The occurrence of march hemoglobinuria in the female subject of this study and in 1 other female reported by Vogt et al.[14] demonstrates that this problem may be encountered in women as well as men.

We suspect that the occurrence of this condition in women is much more frequent than the paucity of available case reports indicates. March hemoglobinuria in men is often misdiagnosed as hematuria due to urinary-tract disease[1]; in women, the condition might be misdiagnosed not only as due to urinary-tract disease but also as consequent to some form of uterine bleeding.

The diagnosis of march hemoglobinuria in this subject was established in accordance with criteria discussed previously.[1] The paroxysmal hemoglobinuria was regularly produced by walking and otherwise never occurred. In the five walks of 1 to 15 miles on which observations were made in this subject hemoglobinuria was always associated with hemoglobinemia. Small, transient increases in plasma bilirubin were also observed a few hours after walks that had produced hemoglobinuria (Table 1). No more than occasional erythrocytes were found even in dark, Burgundy-red urine specimens. The clinical, as well as laboratory, characteristics of the paroxysmal hemoglobinuria in this subject were distinctly different from those of the chill or cold (syphilitic and nonsyphilitic), and nocturnal types, and from favism and myoglobinuria.[1] The negative Donath–Landsteiner and blood Wassermann tests excluded paroxysmal hemoglobinuria from chilling (syphilitic type); the absence of cold hemagglutinins in the blood excluded nonsyphilitic hemoglobinuria due to cold.[29, 30*] Attacks of hemoglobinuria were not associated with the ingestion of fava beans. The spectrophotometric findings that the pigmentation of the plasma and urine was due to hemoglobin differentiated the condition from myoglobinuria.

Grossly visible hemoglobinuria occurred in this subject after walks when the plasma hemoglobin became elevated to approximately 50 mg. per 100 cc., as has been found in other cases of march hemoglobinuria.[1] The total amount of hemoglobin calculated to be liberated into the plasma during these walks of 2 or 3 miles varied from 1.2 to 1.6 gm., equivalent to the hemoglobin of only approximately 9 to 13 cc. of her blood; the calculated amount of hemolysis during the unusually prolonged walk of 15 miles in four and seven-tenths hours was equivalent to approximately 10 gm. of hemoglobin, or the hemoglobin of approximately 80 cc. of the subject's blood.

The number of attacks and the calculated total amount of erythrocytes destroyed during each attack of hemoglobinuria in the course of the daily life of this subject, as in other studied cases,[1] were insufficient to cause anemia. March hemoglobinuria has not been found to cause anemia in any reported cases. The slight anemia exhibited in this patient was probably dietary in origin, for it disappeared when she took ferrous sulfate for a month and recurred later when this medication was discontinued.

The mechanism of hemolysis in march hemoglobinuria is not known. That the hemolysis is entirely intravascular, not massive enough to cause anemia, and in some cases is dependent upon posture is apparently established.[1] It also appears evident from the more extensively studied cases of march hemoglobinuria that within certain limits the total amount of hemolysis increases as the distance walked increases[1] (Table 1). Evidence was gained, in the instance of an unusually prolonged walk in the subject of this report, that the rate of hemolysis during walking may diminish considerably after a certain point if the walk is sufficiently prolonged.

As previously reported in other subjects with march hemoglobinuria only approximately 5 to 20 per cent of the hemoglobin released into the plasma becomes excreted in the urine.

Several investigators[1, 4, 12] have treated their subjects with march hemoglobinuria with ascorbic acid and have obtained variable results, some of them favorable; since the course of march hemoglobinuria is variable and spontaneous remissions common, it is extremely difficult to evaluate the effect of therapy in this condition. For instance, in 2 of our patients described in 1941[1] and seen again recently, the condition cleared up a few months after its onset and never recurred in spite of severe exertion.

Summary

Clinical, biochemical, spectrophotometric and physiologic observations established the diagnosis of march hemoglobinuria in the young woman of this investigation. In accord with her history, short walks under observation gave rise to the

*The diagnosis of paroxysmal hemoglobinuria associated with cold hemagglutinins[20, 21-23] was considered initially because of the possibility that the patient had a viral infection eight weeks before the onset of hemoglobinuria.

passage of red urine pigmented by dissolved hemoglobin and associated with hemoglobinuria. On the other hand, the urine obtained at rest, barring an immediately preceding walk, was always normal in all respects. The clinical characteristics and laboratory findings in this subject ruled out paroxysmal hemoglobinuria due to chilling (syphilitic and nonsyphilitic types), paroxysmal nocturnal hemoglobinuria, myoglobinuria, favism and acute hemolytic anemia.

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PSYCHIATRY IN GENERAL PRACTICE—SOME ASPECTS OF FEAR*

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AMONG general practitioners many "old-timers" have intuitively done magnificent work with their nervous patients, whereas many others in younger generations have often felt baffled by psychiatric problems. For a better understanding, some aspects of fear, as it occurs in the doctor no less than it arises to plague everybody else, including psychiatrists, should be considered: what it is, how it may operate to handicap one's practice of medicine, how it may be dealt with in a patient and how knowledge of it makes for better management of psychiatric cases.

Throughout all human history the story of mental disease is stark with heavily emotional mystery. Century after century rolled on, but the sages thought only in terms of "casting out evil spirits"; the hapless patient was possessed of the devil. Only three hundred years ago the Puritans tried drowning the devil by dunking the patient in a well until air bubbles stopped. If the patient failed to survive this treatment, Satan had too firm a grip on the poor soul. In these days of enlightenment one no longer speaks of casting out evil, but the patient is still dunked in a bath of electroshock. It is comparatively a much refined, better controlled treatment, and research is beginning to find hopeful clues toward understanding of its limited, definitely beneficial effects, but the whole thing is still pretty mysterious because knowledge is so slim.

Although physical illness was once a mystery too, and still is so regarded among primitive tribes, its secrets have yielded to logic with such success that time alone is needed to solve remaining problems. Fear in this direction is gone. The veil of mystery in medicine has been well parted.

But, in contrast, physicians have yet to gain sufficient mastery of psychiatry to feel any real confidence. Like their forebears, both physicians and laity, they must in all honesty admit to a sizable residuum of mystery-laden fear of mental illness.

This basic fear is of the same order as the fear of a lightning bolt, no matter how brave or erudite one may be, and for the same reason — one does not know for certain just what is going to happen, or where, or when, or why. Man fears the unknown. Notable advances indeed have been made in psychiatric knowledge, but not enough to create any comforting assurance to bolster very real fears in the face of this omnipresent potential "lightning" that may strike anyone hard, and does strike frighteningly often.

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Why is it, then, despite the perfect flood of nervous cases, that many physicians appear to have difficulties with them? One fundamental answer to this question may lie in the doctor's own basic fear of the unknown, the mysterious.

Perhaps a characteristic reply to this challenge might be: "I am aware of no such fear myself. And since there does not seem to be too much known about psychiatry anyway, I simply have to by-pass nervous ailments if I can."

But it is quite possible that one is not especially aware of such fears, and the louder the denial, the more obvious it becomes that inward quaking is there. "The Lady doth protest too much, methinks" quoth Hamlet. Much goes on deep inside that escapes attention but that to others may be clearly revealed by actions. Words sometimes belie acts.

A doctor's reactions to a known disease like appendicitis may be quite different from those he experiences when confronted by mental illness. He does not know what the appendix is for, but he does not care because its removal does not matter. He knows it for a harmless, apparently useless adnexus of bowel tissue that stays forever put unless it gets infected. He knows that infection is caused by bacteria, how it acts, and what will happen if it is left unchecked. He knows how to combat this infection by surgical removal, which is almost completely effective. The doctor knows appendicitis, bears it in mind, is alert to find it in his patient and feels perfectly comfortable in his command over the situation.

But when a nerve case enters the scene, the picture is apt to be quite different. The doctor may be baffled, confused, unsure of anything. Diagnosis is a puzzle, etiology, pathology and psychopathology are a mystery, and treatment procedure is completely obscure. The doctor is in doubt; doubt arouses anxiety, and anxiety is fear.

Neurosis is not so neatly packaged and labeled as average ills. Too often its physical symptoms are so like those of organic disease as to mislead the doctor into endless, fruitless and baffling physical examining. Trying hard to avoid "that mental thing," he clutches eagerly at diagnostic variables, anomalies and deviations from normal findings. He wants to find "something physical" no less desperately than his patient, who eggs him on to take another x-ray film to see if perhaps the gall bladder is affected. His professional pride is challenged to win the glory of finding an obscure organic rarity.

If the physician tries timidly to face his patient with "that mental thing," he is apt to be soon di-

verted back to another round of laboratory testing to rule out the new complaint. Or if he bludgeons his patient with "it's your nerves," off goes the patient to somebody else who will be more "understanding."

So the doctor unskilled in psychiatric lore may be baffled from start to finish with such cases. Even if diagnosis seems fairly obvious, management of the case finds him uncertain how to proceed. And uncertainty breeds fear. Fear of what he is dealing with; he is afraid his patient may leave in a huff and is unsure how to advise.

Before this thesis of fear is developed in greater detail, it should be emphasized that carefully made physical examination, being the mark of a good general practitioner, will never be slurred over without possibly disastrous results, as illustrated below. Undulant fever may parade as neurasthenia, anxiety states may closely resemble peptic ulcer, brain tumors sometimes present themselves first as confusional depression, and neurotic patients may also suffer with concurrent organic disease. Apart from these considerations, a most telling step psychologically in psychotherapy is a physical examination. The patient then feels more assured of his doctor's authority. Cancer and other disease phobias absolutely require physical examination at the outset. But, this done, what next? Here is a case of nervous disorder.

Because everybody fears mental illness patients fear to go to a psychiatrist or to a mental hospital. It seems a supreme threat to personal dignity. And the doctor, feeling likewise, is loath to expose his embarrassment by facing his patient with a diagnosis of mental illness, or of any proposal that psychiatric treatment may be indicated.

But there is more to the doctor's fear than these. Whatever a patient's illness may be, the doctor inevitably enters personally into that illness to some extent himself. Whether he has ever had appendicitis or not, he knows personally how it feels to vomit and to have pain in his belly. If he has never had pneumonia he knows by long observation how it must feel to be out of breath, half-drowned and racked with fever and pain. Furthermore, he knows the consequences of illness — its dangers, travails, chances. In short, the doctor cannot avoid identifying himself with his patient.

All this is precisely as true of mental illness. Every doctor has experienced some of the symptoms common to nervous disorders — anxiety, depression, tension, "dish-rag" fatigue, headache, pain in the neck, indecision, insomnia and feelings of inferiority, suspiciousness, guilt, shame, hostility. Especially if he himself has been long burdened with vague, sometimes disturbing rumblings of personal woe, but has not yet been forced to call a spade a spade, he will be reluctant to look squarely at his patient's illness. Introspective as a lot, some doctors shield their vulnerability with a hard-boiled shell. Like whistling in the dark, it helps to keep up morale when fear is close by.

A major psychologic principle underlies the doctor's or, for that matter, anybody's reluctance to face up to nervous ailments. There appears to be a sort of mental censor or watchman at the gate of the unconscious who guards and protects the peace of one's civilized self from the surgings of primitive instinctive impulses. By this mechanism one "forgets," pushes down, represses and keeps out of mind things that would be disturbingly unpleasant and painful to contemplate — feelings, thoughts, impulses, fears and angers that would clash with one's smug idea of himself if they got loose.

The more artificial and contrary to nature civilized society becomes, the harder the censor mechanism has to work overtime to help keep up the façade of equanimity. The doctor in particular lives in just such an overcivilized state. He is supposed to be polite, gentle, patient, supremely tolerant and kind at all times toward his patients, who feel almost perfectly free to whine and complain to their hearts' content. The long-suffering doctor must suppress his own righteous wrath. He must persuade himself and his patient that he stands above ordinary mortal "weakness." He must try to act brave when actually he is scared stiff.

So, when confronted with a case of neurosis or psychosis, the untutored physician automatically goes "on guard." He shies from clear duty by hunting avidly for organic scapegoats where really there are none, and when forced to the truth he self-consciously blunders miserably through the job of trying to help his nervous patient, sometimes doing more damage than good. Quite unwittingly, he is prevented by his own emotional conflicts from being useful.

A doctor can do a better job who understands how strong feelings repressed into unconsciousness create disturbances both of physiology and of thinking attitudes, producing anything from paralyses of functions to gross delusional states, and how with proper release of these emotions normal personality is restored.

The following case of post-partum nervous breakdown may serve to illustrate these points:

Mrs. B., a 22-year-old woman, had a nervous breakdown when her first child was 5 months old.

Her family background had included an ambitious mother, who had pushed her into marriage, and an overprotective father, on whom she was excessively dependent. She had been unready for married life and terrified at the prospect of pregnancy, in spite of the reassurance offered by her affectionate husband. Added to these doubts was a feeling of guilt over her resentment of motherhood before and after her child was born. Her difficulties culminated in an almost irresistible impulse to do away with her child, and the ensuing emotional strain and suppressed tension finally resulted in

an attempt at suicide, followed by a profound depression.

This story of surface data illustrates how nervous illness develops from a chain of past experiences — an important fact. Investigation of the case revealed added substance to the drama. Because her parents were not happily adjusted, the patient had grown up in an emotionally pinched atmosphere, with her father paying her more attention than a man happy with his wife would. This, of course, inspired jealousy in the mother, who tried to cover her feelings with oversolicitude for her daughter's welfare. Thus smothered with fond and "pseudo-fond" overaffections, from both of which she instinctively felt constrained, the girl had been held back from developing normal adult capacity to give of herself to others. Diffident, dependent and inhibited, she could not voice her conviction that she was not yet ready for marriage. Caught in a conflict between trying to be a "nice" girl who did the "right" and "approved" things and her own childish feelings, she sought to maintain emotional equilibrium by burying her resentments against fate as fast as they arose.

She did not want to leave her father, she was no match for her husband, she had never bought groceries, and she did not want to carry a baby — all these choked resentments finally burst in a flash of impulsive rage to kill the child who symbolized her bondage.

Because she became too depressed to be able to communicate, electroshock therapy was given to restore the "nice girl"; then after the usual aftermath of temporary memory lapse had worn off, she was encouraged to talk. As she gradually gained confidence and began to release minor inhibitions successfully, she one day blurted out her awful secret — her criminal impulses. Other repressions too came out; her fears of sex, her resentment of her mother's pushing and her childish worship of her father. All this took time, patience, perseverance and was painful for her to face. But with it she gained perspective, vented her feelings and went home more of a woman.

Thus, it is seen how post-partum breakdowns begin really before marriage, or before pregnancy. Alert obstetricians can often detect a gathering storm, which if treated wisely can be averted. It is worth while to scrutinize the emotional status of young mothers.

Broadly speaking, with variations usually far less dramatic, this sort of thing happens to men as well as to women. As military experience made clear, nervous breakdown can be formulated thus: basic personality plus predisposing factors plus stress equals strain. Strain of sufficient degree in intensity or duration creates a break. Depending on all factors involved, the breakdown varies from insidious onset of symptoms of personality disturbance to dramatic, sometimes violent disruption. No man is exempt from this squeeze combination.

People's personalities often do not grow up on all fronts at the same rate. Part of the child in everyone may tarry on long after bones are set. Violent feeling is natural to childhood, but incongruous in adult experience. Many child-bred attitudes persist in mature years. When a clash between these and current demands becomes severe, when the child side refuses to play adult ball, all sorts of secondary childish emotional disturbances appear. To experience raging anger or stark fear is normal for the child, but the adult's dignified aplomb is horribly upset by such seething waves.

This contrast is so jarring that every one, doctors especially, learns to keep strong feelings bottled up. A cantankerous patient stimulates the little boy in the doctor to feel like punching him on the nose, but most doctors are so well disciplined or so repressed that they hardly recognize the annoyance.

It is healthier to be aware of angers and fears, and to dissipate them safely by "kicking the cat" before getting home where otherwise the poor innocent wife might be the victim of pent-up tensions.

Psychotherapy is thus a definite method of treatment that seems to be grounded on well demonstrated principles and has proved of practical value. It is based on the principle that psychopathology arises as an end result of logical progression of factors, and can be understood as these links in the chain become known.

The purpose of psychiatric examination is to determine the presence of nervous disorder and secondly to assess what sort of treatment is indicated by the patient's immediate status. The question is whether he possesses personality equipment conducive to psychotherapy, and is in sufficiently communicable state to profit by its application. If not and if his attitudes are too rigidly set, hospitalization for further safe observation is the best alternative. There, shock therapy can be safely applied in an attempt to restore communication and to relieve the rigid status.

The objects of psychotherapy are by whatever process to uncover the pertinent factors involved, to bring about release of pent-up emotional tension and to re-educate the patient to a healthier way of living. To some extent all three of these are interwoven in every treatment hour.

The first step is the keystone without which the arch cannot be built. Unless the patient develops confidence in his doctor, no good is likely to occur. Children and nervous people cannot be fooled; they are supersensitive to one's real thoughts and feelings, which no amount of glib talk can hide. Therefore, complete unadorned truthfulness is mandatory. To say "I don't know" is more inspiring than all high-sounding words or examining technics combined.

The object of the first step is to start the patient talking. No patient will confide his heart to any-

one he does not honor, respect and feel sure will understand. An attitude of genuine interest and professional concern helps, but fidgeting, impatience, and personal discomfiture debar one from hearing the true story.

Secondly, with gradually unbridling talk, tension begins to slack. In some cases it will rush out in the first interview, giving vast relief. But more often not. Should the story come out in a cool, detached state, all the facts in the world will yield small improvement. It is the emotional content that counts. Telling a child that fire burns proves nothing until the heat is felt. Going over the story a second time, together with a little judicious needling, may bring forth the purging emotions.

Thirdly, when the story is laid bare in emotional dress, re-education may begin. Attitudes are revised as experience can be reviewed with calm reason. The patient finds that he cannot possibly escape feeling how and what he does, but for future healthy living learns to recognize and discharge emotions outwardly through innocuous expression. Instead of pretending that his devilish urges do not exist, he can appraise them for what they are, and before repression makes them monstrous. He learns that emotions are reflexly aroused and are therefore neither right nor wrong; morals begin when he consciously reacts to them.

In rough summary, then, psychotherapy is a tool used to ferret out facts, release malignant emotions and achieve mature re-education — in other words, to synthesize a better integrated personality. Like all tools, psychotherapy has limitations. It yields best results with people who are reasonably intelligent, who really want to get well and who are sufficiently close to reality to make communication with the doctor possible. The patient must further possess basic potentials of normal personality.

There are people who cannot be expected to benefit from psychotherapy except perhaps in partial degree. Some of these are as follows:

Those of low intelligence. Being limited in capacity to comprehend new ideas, or even to express their own, communication via language with the doctor is severely handicapped. The doctor can neither understand nor make himself understood.

A good many people for all practical purposes simply do not seem to want to get well. A horse can be led to water, but he cannot be made to drink. Nor can a person be made to grow up and get well if he won't. This category includes a sizable group of very chronic neurotics — fussy old maids and crotchety hypochondriacs. And another is a large group of people with inadequate, psychopathic inferior feelings who do not appear to have sufficient qualities to achieve anything resembling normal personality. They cannot get well.

If a person's thinking has become too rigidly abnormal, whether it is manifested by schizophrenic delusions or obsessional ideas of reference, paranoid beliefs or manic-depressive moods, ordinary psychotherapy is a dull tool to use except in most skillful of hands.

Can the general practitioner do anything useful for these groups of people? Yes; and good things are being done every day. Among those of lowly intelligence, a pattern of nervous maladjustment to be found behind many a presenting physical complaint springs from ambition in excess of capacities. If it can be learned how this discrepancy came about, kindly, fatherly advice can help a natural janitor to forget about being president and to find pride and joy in his proper work. In some cases it will be found that the family was trying to make a silk purse out of a sow's ear.

For the patients with chronic neurosis, general practitioners may not realize how excellent a service they perform. However trying some of them may be, strangely enough most are far from useless members of society; indeed, some may occupy high positions in business and the professions. Once it is realized that their annoying complaints really signify emotional misery from which there seems no earthly escape, one's sympathies are aroused to comfort and ease their pain. The doctor's "pink pill" or its equivalent sustains many a wretched soul who without it would founder, for it represents not so much intrinsic relief as a medium of exchange whereby the patient profits really from the doctor's sincere devotion.

There is one other stimulus to keep interest alive, as illustrated by the case of a severely hypochondriacal real-estate man who had been hospitalized in a private sanatorium for years, complaining of abdominal pains along with 50,000 others. One day he had a gastric hemorrhage, but not until then had anyone bothered to discover his long-established ulcers. So, because patients with chronic neurosis may also have physical diseases, it can be a fascinating game to single out organic disease from a variety of neurotic complaints. It takes wisdom and nice judgment to examine enough and yet not so much as to fan the neurotic flames, and to decide that the patient must be carried on a morale-sustaining basis and that his neurosis cannot be improved by direct psychotherapeutic attack.

The general practitioner who has sufficient basic understanding of psychiatric medicine to be free from fear of it himself will refer to a psychiatrist or mental hospital all neurotic and psychotic patients who seem to require specialized treatment. For his calm, assured manner will quiet his patient's fears of the unknown. The patient will approach psychiatric treatment with hope inspired by his doctor, who has shown that he knows the way.

SUCCESSFUL POST-MORTEM CESAREAN SECTION FOLLOWING DEATH FROM PULMONARY TUBERCULOSIS*

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SUCCESSFUL post-mortem cesarean sections performed on patients who have died from various causes have not been frequently reported in the past. In all the medical literature there are fewer than 100 cases recorded. Rescuing a living baby from a patient who has died of pulmonary tuberculosis is relatively uncommon, one of the earliest successful cases having been described by Huguier[1] in 1829. The following case is presented because of the scarcity of such reports and because it is believed to be the first in this country.

CASE REPORT

B. W., an 18-year-old Negress, was admitted to the Rutland State Sanatorium on February 14, 1950. She had been born in the South and had lived there until 4 years previously, when she had moved to Boston to do domestic work. Her past history was noncontributory, and there was no known exposure to tuberculosis. The last menstrual period had begun on September 28, 1949, and the expected date of delivery was July 5. This was her first pregnancy. Her present illness had begun in October, 1949, with hoarseness and cough, which persisted until she sought medical treatment in January, when she was admitted to another hospital, where a diagnosis of laryngeal and pulmonary tuberculosis was made.

Physical examination revealed a patient who appeared to be quite ill, was emaciated and was an estimated 4 months pregnant. X-ray study showed marked involvement of the left lung, with infiltration and multiple cavitation in the upper half, but the right lung was fairly clear. Examination of the blood disclosed a red-cell count of 3,070,000, with a hemoglobin of 10.5 gm., and a white-cell count of 11,500, with 78 per cent neutrophils, including 8 per cent band forms, 8.5 per cent lymphocytes, 9.5 per cent monocytes, and 3 per cent eosinophils; the sedimentation rate was 1.93 per minute by the Rourke–Ernstene method (normal, 0.40 mm.), the icteric index 3, and the hematocrit 32.5 per cent. The blood Hinton test was negative, and the urine was normal. The sputum was positive on smear for tubercle bacilli.

The patient appeared to be chronically ill. Her weight was 104½ pounds (usual weight, 117 pounds). The blood pressure was 110/78. Examination of the chest showed dullness in the upper part of the left lung, with increased breath sounds and crepitant and moist rales throughout the lung. The fundus of the uterus was enlarged to one fingerbreadth below the umbilicus. The larynx showed slight edema of the arytenoid area.

The patient received 2 gm. of streptomycin daily at another hospital from January 21 to 27 and 1 gm. daily from January 28 to February 14. This was continued here until March 3, by which time she had received a course for 6 weeks. Pneumothorax on the left was instituted on March 3, and pneumonolysis performed on April 24. During this procedure it was noted that there were more than a dozen adhesions holding the upper lobe to the chest wall, and most of these adhesions had a subacutely inflamed appearance. However, lysis was performed successfully, and the upper lobe appeared to collapse. After the operation the lung re-expanded quickly and adhesions re-formed so that it was not possible to continue the pneumothorax, which was abandoned by May 4. During the first course of streptomycin there was some improvement in the laryngitis and difficulty in swallowing and the temperature subsided from daily readings of 100 to 101°F. to normal. During the next 3 weeks, however, the symptoms became aggravated, and a second course of streptomycin was begun on March 30, with 1 gm. daily. In April the organism showed resistance to the antibiotic. The clinical and roentgenologic course continued to go downhill although the progress of the pregnancy appeared normal.

After the patient had been here almost 3 months and toward the end of her 7th month of pregnancy she suddenly had a hemoptysis of about 25 ounces on May 6. On the following day there was another hemoptysis of 20 ounces and during the next 2 days small amounts of blood continued to be coughed up. At noon on May 10 she had a severe hemoptysis, which could not be influenced or controlled by medical means, and she died at 12:10 p.m. The heart beat was no longer audible, and the fetal heart beat, which had previously been distinctly heard, also became inaudible. However, a distinct kick by the fetus was felt through the abdomen, and an immediate cesarean section was performed. One incision was made through all the layers, including the uterine musculature, followed by blunt finger dissection of the remaining muscle fibers of the uterus to rupture the membranes, allowing the fetus to be quickly delivered. The baby was born within 5 minutes from the time death was pronounced. The umbilical cord was tied and cut, and the infant resuscitated without unusual difficulty by the removal of mucus from the nose and throat and by body stimulation, including contrast dips in warm and cold water. When the baby breathed and cried it was wrapped in cotton batting and blankets, placed in an improvised incubator and immediately transferred to another hospital.

Post-mortem examination of the patient performed 6 hours after death gave few significant findings. A large portion of the epiglottis was destroyed by the tuberculous process. The false vocal cords and the vestibule showed considerable papillary thickening of the surfaces, with some ulceration. The true vocal cords were likewise involved. There was a swelling in the esophagus at the upper margin of the aryepiglottic fold, measuring 2 by 1 cm. in its greatest diameter, that was fluctuant, but the surface was not eroded. The upper lobe of the left lung was adherent to the chest wall, but the base was free. The trachea and bronchi showed no ulceration. The major bronchi and their branches revealed a large quantity of clotted blood. The upper lobe of the left lung was collapsed and fibrosed and contained six cavities ranging from 1 to 6 cm. in diameter. Methylene blue injected through a pulmonary artery was found in one of the smaller cavities. The larger cavity, however, also contained clotted blood. The lower lobe disclosed numerous tuberculous nodular areas. There were also areas of consolidation. No significant gross lesion was seen in the right lung except for the areas containing aspirated blood. The gastrointestinal tract showed a few tuberculous ulcers in the terminal ileum. The pelvis and ureter of the left kidney were greatly distended, giving evidence of hydroureter and hydronephrosis. On section of the left kidney, the pelvis and calyxes were all dilated, and the cortex was considerably reduced in some areas. No tuberculous lesions, however, were found. The placenta was intact and still attached to the superior and anterior portion of the fundus. No tubercles were seen.

An interesting though incidental and unusual autopsy finding was observed. After the lung had been removed from the body, approximately 6 hours after death, there was seen near the base of the right lung at its periphery a peculiar rhythmic contraction, which involved an area about 2 cm. in length. These spontaneous contractions continued for approximately 3 or 4 minutes, after which they were again produced with stimulation by slight massage and irritation by sharp stimuli. Most of the contractions appeared to occur in a cord or channel, the remaining adjacent lung parenchyma becoming depressed with each contraction. The spontaneous contractions and also those induced by artificial stimulation

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were observed for a period totaling about 5 or 6 minutes. These were recorded with a motion-picture camera.

The premature male infant appeared to be the result of about a full 7 months' gestation and weighed 4 pounds at birth. Physical examination was within normal limits. He was kept in an incubator and given oxygen during the first 3 weeks. After an initial loss of 3 ounces he gained well with a formula and also received concentrates of vitamins A, C, and D and iron. He was also given daily clyses of 5 per cent glucose for the first 3 weeks. An upper respiratory infection developed during the 5th week, with slight fever and nasal discharge, but responded to penicillin injections at 3-hour intervals for a period of 5 days. A white-cell count and differential count were normal but repeated red-cell counts showed an average of 2,400,000, the hemoglobin ranging from 45 to 60 per cent (Sahli). For the secondary anemia the infant was given a transfusion of 25 cc. of citrated blood when he was 2 weeks of age, and because the blood count did not improve appreciably, he was given another transfusion of 50 cc. of citrated blood at 6 weeks of age. After this, the red-cell count rose to 3,500,000, with 65 per cent hemoglobin (Sahli) by the time he was discharged. He gained between 4 and 10 ounces per week, and at the time of discharge from the hospital at the age of 9 weeks he weighed 8 pounds, 2 ounces, which was more than double his birth weight. Patch skin tests performed at 2 and 10 weeks of age were negative. At this writing the infant is 2½ months old, weighs 9 pounds, 4 ounces, and seems to be normal in all respects.

Discussion

Post-mortem cesarean sections have been advocated and carried out for many centuries. Their performance was encouraged in the Talmud, and reference has also been made in the *lex regia* of Numa Pompilius, the second king of Rome. This old Roman law is frequently mentioned as serving as a precedent in the medicolegal discussions of this subject. Later, in Austria, an old law made it compulsory for the doctor seeing the corpse of a pregnant woman of six months' or more gestation within one hour of the time of death to do a post-mortem hysterotomy.[2] This was done in the days of the Romans so that the baby and mother might be buried separately, and during the Christian Era it was carried out so that the baby might receive the blessing of baptism. Throughout the centuries of the Christian Era there were no available medical reports concerning successful results of this procedure. One cannot find such cases until the last century. During the nineteenth century Pfaff[3] states that of 331 post-mortem cesarean sections performed, only 6 or 7 living babies were delivered. During the first fifty years of the twentieth century there has been greater success. Purdie[4] summarizes the successful cases of this century until 1945. Since then 3 more by Johnson and Frank,[5] Dobbs[6] and Simmons and Ellis[7] have been added. There are approximately 80 cases of successful post-mortem sections thus far during this century. This represents a number larger than the aggregate during all previous centuries. The cause of death in the majority of all cases was some complication of pregnancy, notably toxemia and convulsions. Other causes include death from cerebral hemorrhage,[8] pneumonia,[9] cardiac failure,[10] dissecting aneurysm,[5] bulbar poliomyelitis[7] and tuberculosis.

The title of most articles on post-mortem cesarean section does not include the cause of death. Of the several hundred found in the Army Medical Library[11] only that by Huguier[1] specifies tuberculosis when this was the disease involved. Written more than a hundred and twenty years ago, this detailed report demonstrates admirably the medical acumen of the author. Fewer than 15 successful post-mortem sections on tuberculous patients are found during this century. Seuffert,[12] Linzenmeier[13] and Roemer[14] offer single cases, whereas, Böhmer[15] lists 4, and Sebold[16] 3, and Kupfer[17] accounts for 6 living babies from 9 cases of tuberculosis among the 100 all-inclusive case reports from 1875 to 1927 (possible duplication of the others). All of these are in the foreign literature not listed by Purdie.[4] Not included as successful cases are babies delivered alive by the operation under discussion but dying soon thereafter.[15-17] Ruge[18] writes of a patient with acute miliary tuberculosis who died two hours after cesarean section, the infant dying at three weeks of age. This case is not considered among the successful ones, and other similar deliveries performed while the patient was moribund[15, 16, 19, 20] are excluded even though the baby may have survived a short or long period.

Even though the death rate from tuberculosis has decreased from 200 to 30 per 100,000 population in this country during the past fifty years, post-mortem cesarean section must be considered in presenting cases. Pregnancy still occurs in patients who have active tuberculosis, and one might expect more of such cases to occur and to be reported with successful results if the operation was carried out. Congenital tuberculosis is notably uncommon. In the largest series of carefully studied cases,[21] it is stated that the incidence is approximately 1.46 per cent. Even this figure may be somewhat high, but the prevalent opinion is that the infant rarely, if ever, contracts congenital tuberculosis unless the placenta is involved with tubercles and even more rarely when bacilli reach the fetal blood stream or the infant aspirates infected amniotic fluid.

Conclusions

I have questioned many of the large and oldest tuberculosis sanatoriums in this country about the incidence of post-mortem cesarean sections carried out on patients who have died from pulmonary tuberculosis, but there have been no cases recorded. Certainly, with an estimated 90,000 patients confined to sanatoriums and rest homes with active tuberculosis, the incidence of pregnancy among the women patients might be significant, and the possibility of a cesarean section at the time of death realized. There is no reason to suspect that the rescued infant may not prove healthy and normal

in all respects whether the death of the mother was caused by pulmonary tuberculosis or other disease.

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MEDICAL PROGRESS

SYPHILIS (Concluded)*

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Benign Late Syphilis

There has been more interest in geriatrics during recent years, but the index of suspicion of syphilis is relatively low when one is faced with the complaints of older patients. It has been claimed that unsuspected and unadmitted syphilis is not uncommon in old age.[115] Syphilis may cause symptoms suggesting any known disease, including the chronic illnesses to which the aged are more susceptible. Serologic tests may be confusing in these situations, especially when the syphilis may be of thirty or forty years' duration and the reagin titer will be low or vacillating from positive to negative and positive again. Examinations of the spinal fluid may also be inconclusive. The danger of reactions and the therapeutic paradox are greater in elderly persons with late syphilis, and treatment should be approached more cautiously. Nevertheless, the discovery of old syphilis and proper therapy may save much suffering and prolong life. Three cases were recently reported in which gummatous lesions developed thirty-three, forty-seven and sixty years after infection.[116] In each case the lesion was associated with neurosyphilis of one form or another. This illustrates that a period of latency of forty years or longer may not be as uncommon in syphilis as the sparse reports in the literature indicate. Elderly patients with gummas may easily be misdiagnosed and are frequently thought to have malignant tumors.

In the earlier stages of latent syphilis (about two years) it is common procedure to use the same therapy schedule employed for secondary syphilis. Combined therapy is also advocated.[117] The serologic response is somewhat less satisfactory, but relapses are less common.

Late latent syphilis has received relatively little study in the penicillin era, but as expected the response to treatment has been slower than with other forms of the disease. It is more difficult to

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ascertain the value of any treatment in the latent stages. A survey of over 2500 patients with late latent syphilis observed for periods of one to nine years or more during the prepenicillin period indicates that the prognosis in late latent syphilis is improved by treatment at any time.[118] There appeared to be steady improvement with increasing amounts of therapy. One should be able to expect at least as much of penicillin treatment.

Active late syphilis of the benign types involving structures not essential to life or vision and so forth includes syphilis of the skin, mucous membranes and bones. Relatively few reports are available on the treatment of these varieties, but the response in general is satisfactory.[119] The amount of penicillin administered is generally somewhat more than that for early syphilis, and the time factor should be extended.

In a report of 3 cases of pernicious anemia complicated by late syphilis, it was demonstrated that 6,000,000 units of penicillin created no adverse effect on the erythropoietic response to antianemic treatment.[120] The reticulocyte response was a third to two thirds of the usually expected value, irrespective of the penicillin, and it was believed that this may have been a consequence of syphilis.

Ocular Syphilis

Syphilis of the eye is considered as an individual topic, for convenience, although all the various stages of syphilis may contribute to the lesions of this organ. That penicillin is an effective, nontoxic anti-syphilitic drug in ocular syphilis is accepted by ophthalmologists and syphilologists alike. Its use in the early and acute lesions of the eye has given encouraging results. It is imperative, however, that the Herxheimer reaction be avoided if possible. The iritis of secondary syphilis responds to penicillin therapy as administered for the secondary stage of the disease.[121] Syphilitic uveitis heals dramatically, inflammation disappearing in one or two weeks.[122] Syphilitic optic neuritis with the choked disk observed in acute syphilitic meningitis shows a good therapeutic result if adequate penicillin is administered early; normal vision is usually obtained.[121, 122]

Primary Optic Atrophy

It has been estimated that 90 per cent of the blindness caused by syphilis can be attributed to the optic atrophy occurring in acquired and congenital syphilis.[123] The importance of early diagnosis is stressed in this review of nearly 400 patients, ranging in age from nine to seventy-five years. Few if any of this group had received treatment in amounts considered adequate according to modern standards. In addition to impaired vision as a symptom of optic atrophy, pain in the legs, diplopia, impairment of adaptation to light and difficulty in distinguishing colors may aid in an early diagnosis. The authors believe the earliest symptom of optic atrophy, preceding loss of central vision and pallor of the disk, is a visual-field defect. The earliest field losses in primary optic atrophy are said to be those of color, particularly red and green. Subsequent to visual-field defects, the optic disk shows some degree of pallor.

It is not possible to restore any vision lost in the process of atrophy of the optic nerve, but if diagnosed early many cases may be arrested by adequate therapy. Syphilitic primary optic atrophy may occur in any form of neurosyphilis. It is exceedingly difficult to correlate spinal-fluid response to treatment with the progress of optic atrophy.[124] Not all patients will respond to treatment, regardless of the method employed. There seems to be great value in penicillin, but the majority of authors reporting groups of patients with syphilitic optic atrophy seem to believe that combined penicillin and fever therapy holds the greatest promise.[121, 122, 124] Penicillin alone has also been advocated.[125] One author believes that vasodilators are of greater importance than antisyphilitic therapy.[126]

Interstitial Keratitis

Another grave treatment problem in ocular syphilis is interstitial keratitis, which also fails in many cases to respond to any of the forms of therapy. A factor that makes it difficult to assay the value of any treatment is the relative slowness of response. Improvement in interstitial keratitis is seldom appreciably in evidence during active treatment. It is also commonly observed that no type of therapy so far devised will prevent an initial attack with certainty, or forestall the involvement of the second eye, or guarantee against recurrence. Intensive penicillin alone has been claimed to be of value equal to or greater than earlier forms of therapy.[122] Most authors, however, believe that combined penicillin and fever therapy is preferable.[121, 127, 128] If proper treatment can be instituted before the keratitis has been active for longer than a month or two, useful vision can generally be restored in about 80 per cent of the eyes affected. Nevertheless, the treatment is still not to be considered satisfactory, and a search for more promising methods is continuing. The management of interstitial keratitis remains one of the greater problems in syphilotherapy.

Cardiovascular Syphilis

The earliest manifestation of cardiovascular syphilis, aortitis, can frequently escape the clinician even though he may exert exceptional diagnostic skill. The diagnosis can occasionally be established by x-ray examination prior to the clinical detection of physical change. Attention has been called to the fact that calcification in the ascending aorta and sometimes in the knob of the aorta is a strong indication of syphilitic aortitis.[129-131] Linear calci-

fication in particular should be considered suggestive of syphilitic aortitis. The finding of linear calcification in the ascending aorta may be of considerable value in a differential diagnosis of aortic insufficiency caused by other disorders such as rheumatic heart disease and arteriosclerosis. A control study of 100 cases of atherosclerosis of the aorta exhibited only 2 per cent with calcification of the ascending aorta, in contrast to 18 per cent of 122 cases of syphilitic aortitis. This study was corroborated by autopsy material. Calcification may also help to differentiate aneurysm from tumor. A still more definitive method of establishing the diagnosis of syphilitic aortitis is by angiocardiography.[132] This reveals rather clearly the gross anatomy of the entire thoracic aorta, and a diagnosis can often be made by the procedure in the absence of conclusive clinical or roentgenographic evidence. Aortic dilatation, irregularity of the lumen, calcification of the ascending aorta, aortic tortuosity, variations in thickness of the aortic wall and the presence of aneurysm can all be clearly shown. An earlier and sounder anatomic diagnosis with consequent earlier treatment of the cardiovascular complications of syphilis should be provided by angiocardiographic studies. This is a highly technical procedure, however, and only applicable when proper facilities and well trained personnel are available.

It is generally agreed that adequate treatment of early syphilis will afford protection against the development of cardiovascular complications in practically all cases. The syphilis campaign that has been underway in the past decade should be reflected in a distinct decrease in the amount of cardiovascular syphilis observed in the years that follow. Even if syphilis is untreated until the diagnosis of syphilitic aortitis is established, the more grave cardiovascular complications could generally be avoided by intensive penicillin therapy. Autopsy studies from many medical centers have confirmed the fact that 80 to 90 per cent of the patients with long-standing syphilitic infections, inadequately treated during the early stages, show pathological evidence of syphilitic aortitis.[133] Aortitis may be completely asymptomatic, and even insufficiency of the aortic valves or aneurysm may be present for long periods before the development of symptoms. These last two complications could nearly always be clinically detected with a careful examination if the patient was under observation. It seems questionable whether electrocardiographic changes pathognomonic of syphilitic heart disease actually exist. In any stage of cardiovascular syphilis, the major problem is avoidance of the Herxheimer reaction and the therapeutic paradox. There is probably no more danger of the latter complication with penicillin treatment than with chemotherapy. Although there was great fear of reactions when penicillin treatment of cardiovascular syphilis first began, there is currently a belief that the therapeutic paradox has been exaggerated.[133] Even the Herxheimer reaction is regarded as a rare phenomenon by one group, who reported a relatively large series (78 cases) of cardiovascular syphilis treated with penicillin in full dosage from the beginning.[134] Other authors describe varying percentages of the incidence of Herxheimer reactions after penicillin treatment of cardiovascular syphilis.[135, 136] The dose administered was 6,000,000 to 8,000,000 units. There is some belief that bismuth treatment should be given prior to penicillin in an attempt to forestall the Herxheimer reaction.[137] In uncomplicated syphilitic aortitis, the progress of the disease can usually be arrested by adequate therapy with penicillin. When aortic insufficiency or aneurysm is present, these complications may possibly be arrested, or their progress may at least be slowed down to prolong life. Patients who have had coronary-artery disease or who are in a state of cardiac decompensation seem to have tolerated penicillin therapy without appreciably more hazard than others.[136, 138] The simultaneous use of penicillin and measures to combat congestive failure is seemingly well tolerated.

The practice of arresting the expansion of aneurysmal dilatation of the aorta by interlacing the enlarged portion of lumen with fine wire has been in use for some time, with relatively satisfactory results. A new approach to this situation has been presented in the form of cellophane wrappings.[139] Arteriosclerotic aneurysms appear less suitable than those of syphilitic origin for this treatment. Fusiform aneurysms of the descending thoracic aorta seem to provide the best results from the cellophane wrapping.

Neurosyphilis

Almost from the beginning of the penicillin era, the drug has been used to a greater and greater extent in the treatment of syphilis of the central nervous system. This was to be expected, since within this field lie the forms of the disease entailing greatest suffering, the most protracted incapacitation, large numbers of cases that have been treatment-resistant and patients who have become totally disconnected from society, with the resulting burden of custodial care. The acute types of syphilis of the central nervous system have responded rather well to penicillin therapy. An interesting report of 80 cases of acute syphilitic meningitis has appeared.[140] Sixty patients had a history of early syphilis, while in the remaining 20, the meningeal symptoms were the first observed clinical manifestations of the infection. Sixty-nine patients had had a serologic test performed within a few days of the time of the diagnosis of meningitis. Eleven were negative. The cerebrospinal-fluid complement-fixation test was also negative in 6 cases. Eighteen patients were treated with penicillin;

the others were all observed prior to the introduction of penicillin therapy. The rate of disappearance of signs of meningeal irritation and of increased intracranial pressure was approximately the same in patients treated with arsenical drugs as in those receiving penicillin. Similar rates of clinical improvement and response in the abnormalities of the cerebrospinal-fluid and blood serologic tests were noted in both groups. The authors believed that approximately 5,000,000 units of penicillin G in a period of seven to ten days is the treatment of choice in acute syphilitic meningitis, but obviously a prolonged follow-up study is required. It has been stated that the treatment of early syphilis with penicillin has considerably reduced the incidence of early neurosyphilis.[141] The same author cautions, however, that a single normal spinal-fluid specimen immediately after the treatment of early syphilis cannot be relied upon. A negative examination four years or more after the primary lesion, regardless of whether therapy has been given, is stated to be good assurance against the future development of meningovascular or parenchymatous neurosyphilis. (This statement may well be challenged.)

In therapeutic assays of the various methods of treating neurosyphilis it has become generally accepted procedure to consider the cerebrospinal-fluid changes as a primary guide to the effectiveness of therapy. The response in symptomatology and physical findings may be delayed for a considerable period, and less reliance is placed upon the clinical features of neurosyphilis as a guide to treatment. Nearly all observers agree that if there is a gradual improvement in the spinal-fluid test throughout a year after treatment, retreatment may not be required. If the spinal-fluid findings or clinical manifestations become worse, retreatment is obviously indicated. If there is no change after a year, retreatment should be seriously considered. In view of the emphasis placed on spinal-fluid findings in therapeutic studies, a review of the four obligatory spinal-fluid tests is apropos. These are: cell count, total protein content, colloidal-gold test and complement-fixation reaction. The cell count is usually the earliest evidence of syphilis of the central nervous system and gives information regarding the inflammatory process. The total protein determination is a further guide to the degree of activity of the neurosyphilis. The complement-fixation test determines the amount of reagin in the spinal fluid and constitutes a means of identifying the specific infection of the central nervous system; it does not indicate the degree of activity of the process. The colloidal-gold test provides information regarding the type of involvement of the central nervous system, such as parenchymatous neurosyphilis or disease of the interstitial tissues. The results of these four tests, interpreted as a whole, provide reasonably accurate information about the syphilitic process in the central nervous system. It is not satisfactory to rely on anything less than the entire group of four tests.

The treatment plans reported in the management of neurosyphilis during the past eighteen months almost invariably include penicillin in one form or another — alone or in combination with other agents. There is still considerable controversy regarding the situation, particularly over whether penicillin alone is as satisfactory as penicillin in addition to fever therapy. There seem to be about equal numbers of advocates of both approaches to the problem, and there are many well qualified syphilologists on both sides of the question.

Penicillin Therapy Alone

Reports from several of the largest institutions in the country have recorded sizable groups of patients with neurosyphilis treated with penicillin alone and in parallel with comparable groups who received penicillin and fever therapy.[90, 91, 142-148] From 200 to 500 patients are included in each series, and they have been followed for periods of two to five years. Early in these studies some patients received as little as 2,000,000 units of penicillin, but in each clinic the amount steadily rose until most institutions are now using 6,000,000 to 10,000,000 units. The time factor is considered important, and there are more and more who advocate extension of the treatment time over periods as long as three weeks or even more. In some cases the authors had stated in earlier reports that the more severe forms of parenchymatous neurosyphilis probably required the addition of fever therapy to achieve success, but have later come to the conclusion that penicillin alone is at least equal to the combined therapy. In calculating effectiveness of treatment, all observers have utilized the spinal-fluid findings as the primary guide, and as high as 90 per cent satisfactory results are reported in some of these groups. When surveyed from the standpoint of clinical effectiveness, the results are more variable; clinical failures are claimed to be as low as 6 per cent in 1 series, but admitted in as high as 75 per cent in such situations as the schizophrenic type of general paresis. When failures were recognized and retreatment instituted with penicillin alone, more than half the retreated patients responded satisfactorily in each group.

The proponents of the use of penicillin alone in the treatment of neurosyphilis are obviously becoming more and more strongly in favor of this approach to the problem as their patients are followed for each succeeding year. The type of penicillin employed seems to make little or no difference in its effectiveness. The amount of preceding treatment seems to matter little unless a full six months of routine metallic chemotherapy has been administered within the year prior to penicillin therapy; this seems to be of distinct value. The repository types of penicillin are slowly coming into greater

use.[90, 91, 147] These more slowly utilized penicillins are being studied now in a dosage of 600,000 units as infrequently as three times a week for periods of three weeks.

It is apparent that there must be at least some small percentage of failures. No method of determining the sensitiveness of the spirochete to penicillin has yet been devised. This makes it nearly impossible to gauge the amount of penicillin therapy required except by a clinical trial-and-error approach. In some groups of patients, there was a remarkably good response to surprisingly small amounts of penicillin treatment. This suggests that a given quantity of penicillin may be just enough to tip the balance in favor of the patient so that the host-resistance factor is able to overcome the onslaught of the infecting organisms. The problem lies in determining the amount of treatment required to accomplish this favorable turn of events. Obviously, it will vary from patient to patient, and no accurate means of settling the question is available.

Combined Therapy

The value of fever therapy in the treatment of neurosyphilis has long been established, and even the proponents of penicillin alone for the treatment of this problem do not deny the usefulness of hyperpyrexia. Several of those authors frankly stated that if retreatment with penicillin was not effective, especially in advanced cases, combined penicillin and fever therapy should be administered. There is an equally diverse and experienced group of observers studying the treatment of neurosyphilis who believe that the combination of penicillin and hyperpyrexia is of greater value than penicillin alone.[149-158] The groups of patients treated are comparable in size to those treated with penicillin alone, and the follow-up periods also extend as long as five years. The amounts of penicillin administered are somewhat lower, most authors reporting a maximum of about 6,000,000 units. They have used relatively shorter courses of fever therapy than were formerly employed. The method of production of hyperpyrexia has most often been malarial fever, but there are those who prefer the induction-hypertherm units, hot blankets and so forth. As few as five to seven paroxysms of malaria may be allowed. When artificial fever is used the minimum seems to be about twenty hours of temperature reaching 105°F. These authors believe that the combined penicillin-fever treatment is decidedly superior to any treatment previously devised. In some groups there were parallel series of patients treated with penicillin alone, but others have merely compared their results with recorded statistics. Some even state that penicillin alone is not as good in its effect as the combination of chemotherapy and fever that was utilized in the pre-penicillin era. Most opinions, however, agree that in the milder asymptomatic neurosyphilis and meningitis, one or two courses of penicillin alone may be considered for preliminary therapy. The authors are all firm in their opinion that the severe parenchymatous involvement and in particular such situations as progressive optic atrophy or severe gastric crises require combination therapy. Some believe that the higher desirability of fever therapy combined with penicillin lies in a greater degree of permanent arrest of the disease. The schizophrenic type of general paresis proved to be the least amenable to any form of treatment, as indicated also by the group favoring penicillin alone. Electric-shock therapy has been utilized with distinct value in more severely psychotic patients, in addition to fever and penicillin.

It thus becomes obvious that there are two opposing schools of thought, still strongly advocating the two types of therapy. Nevertheless, they are closer together than they were a year or two ago. Those favoring penicillin alone admit the occasional advisability of fever therapy, and those proposing combined treatment are willing to use initial courses of penicillin in many cases of neurosyphilis.

It seems safe to say that there is rather general agreement regarding the use of penicillin alone in asymptomatic neurosyphilis and acute meningosyphilis. The amount of penicillin to be used should be approximately 9,00,000 or 10,000,000 units and preferably spread over a period of not less than three weeks. In parenchymatous neurosyphilis, if not far advanced, preliminary therapy with penicillin alone may be seriously entertained. When pronounced degenerative changes are obvious, it is questionable whether fever therapy should be delayed. Certainly, no form of therapy can restore degenerated nerve tissue, and further loss of function should be avoided if possible by the use of every effective means available. In all probability 10 to 20 per cent of patients, or perhaps more depending upon the type of neurosyphilis, may need to be retreated. Approximately half these more advanced cases may respond to additional therapy. Still more effective means of dealing with the remaining resistant cases are yet to be devised. Nevertheless, the prognosis for any type of neurosyphilis is distinctly better than it was as recently as ten years ago.

When the various types of neurosyphilis are considered individually, it is clear that the earlier manifestations now seem quite readily amenable to therapy. Meningovascular syphilis was found to respond poorly to penicillin alone in one series.[147] Tabes dorsalis, especially advanced cases with optic atrophy and severe subjective symptoms, is more difficult to deal with and probably should have combined therapy at the outset.[151, 153, 159] There are complexities in evaluating the treatment of tabes that make it difficult to recommend a single procedure that will be applicable to all patients. There seems to be no consistent correlation between

laboratory and clinical response in this variety of neurosyphilis.

When therapy for general paresis is evaluated, the variations in this type of neurosyphilis should also be taken into consideration. Schizophrenic dementia is the most difficult of all.[152, 154] It has been suggested that the basis for comparison of different methods of treatment should be related to the assorted types of psychosis. On the other hand, a survey of over 1400 cases of neurosyphilis leads another author to place but a limited value on the significance of symptoms in the evaluation of treatment in paresis.[160] He believes that the lack of symptomatic response to therapy does not constitute a treatment failure, or indication for retreatment, provided the spinal-fluid abnormalities are regressing toward normal. In other words, the major criterion for the effectiveness of therapy is its ability to produce and maintain serologic negativity, regardless of the psychiatric status of the patient.

It has been a widespread observation that in nearly all varieties of neurosyphilis, once the spinal-fluid aberrations have returned to normal, a serologic relapse seldom occurs, if adequate therapy had been administered. This is perhaps the most encouraging evidence of the effectiveness of penicillin either alone or in combination with fever therapy.

A more complicated system of combined therapy for neurosyphilis included the use of penicillin intramuscularly and intraspinally with fever and bismuth therapy.[161] Although the series of patients is small, the author claims most favorable results with this four-way treatment program in patients with severe neurosyphilis. Intrathecal medication is not to be undertaken lightly, however, and a wide variety of complications have been reported after intraspinal medication, even when the nervous system is presumably free from disease.[162] Spinal injections may also precipitate the appearance of symptoms and signs of some neurologic disorder previously latent. It is possible that there will be some neurotoxic action of penicillin after intrathecal injection. Severe reactions have been reported with this type of treatment, and the impression should not be given that intrathecal therapy with penicillin is desirable for neurosyphilis.[163] This seems particularly true in view of the favorable reports of therapeutic trends in neurosyphilis referred to above.

An excellent delineation of the technical aspects of therapeutic malaria is available for those who desire to use this modality in the treatment of neurosyphilis.[164] This information is particularly useful when resistance to inoculation with malaria interferes with a treatment plan. The use of malarial fever has decreased since the introduction of penicillin, and there may be occasions, even in metropolitan areas, when a supply of *Plasmodium vivax* parasites will not be readily available. A technic of preserving viable *P. vivax* for as long as five or six months by a rapid freezing method has been reported.[165] There was no evidence that the freezing affected the final result of inoculations. The incubation period, when it could be accurately determined, varied between six and twenty-two days. The clinical course of malaria resulting from inoculations with preserved parasites did not differ in any way from that seen after the direct inoculation with whole blood.

There are some patients with tabes dorsalis who are so severely degenerated that their symptoms respond to no form of medical therapy. When gastric crises are the predominant complaint, alleviation of the nausea and vomiting may be almost impossible. Vagotomy has been employed in an attempt to remedy this situation.[166] Four patients with intractable gastric crises were selected for this treatment. The operation did not relieve the pain in any patient, but it did stop the vomiting in 3, and 2 of them maintained their improvement for the year that they were followed.

Lumbar-Puncture Headache

Headache is the most frequent undesirable secondary effect of spinal puncture. The "leakage" theory is at present the most widely accepted. This is thought to lower the pressure sufficiently to permit caudad displacement of the base and posterior parts of the brain, with tension on the anchoring structures, particularly the tissues around the large arteries at the base of the brain. The feature that distinguishes this headache from all others is its exacerbation when the patient sits up and the relief obtained upon lying down. The injection of 30 to 50 cc. of isotonic solution of sodium chloride into the spinal canal has been found sufficient to restore the pressure to the normal or upper normal range and to abolish headache.[167]

A study of 1658 spinal punctures indicated that the use of prepuncture sedatives did not decrease the incidence of post-puncture headache.[168] This de-emphasizes the theory of emotional and psychologic factors that some have brought forward. There appeared to be no appreciable difference in the occurrence of headaches among those who were active soon after the puncture and those who were kept recumbent for twenty-four hours. There was an over-all incidence of post-puncture headache of 29 per cent. Among 500 of these patients who had had lumbar puncture done for inducing spinal anesthesia, only 7 per cent developed a headache.

The value of reasonably prompt examination of the spinal fluid is illustrated by a study showing that total protein values in spinal fluid are generally higher in mailed specimens than in identical specimens tested immediately.[169] It also appeared that the values showed a greater elevation in spinal fluids mailed in nonsterile, cork-stoppered tubes than in specimens sent in sterile vacuum-type tubes.

It was further brought out that the complement-fixation test was much less reliable when the spinal-fluid specimens were mailed in nonsterile, cork-stoppered containers. Whereas the control portion of the specimens were 88.7 per cent negative, those mailed in nonsterile cork-stoppered containers were only 45.3 per cent negative. This is of particular importance in view of the fact that spinal-fluid examinations are not as simply and quickly repeated as blood serologic examinations.

Syphilis in Pregnancy

There is no other field in the management of syphilis in which penicillin has provided such excellent results as in the prevention of congenital syphilis. This treatment has been demonstrated to be almost 100 per cent effective, and the most comforting feature of the situation is the fact that penicillin almost invariably prevents congenital syphilis even when administered in the last weeks of pregnancy. It was known that chemotherapy would nearly always forestall congenital syphilis if it was begun during the first trimester of pregnancy and carried through properly to term.[170] Careful administration of arsenic and bismuth to the pregnant woman had come to be regarded as less of a hazard, and the question was arising whether retreatment was required with each succeeding pregnancy. The advent of penicillin, with even better results, coupled with less toxicity and its effectiveness at any time during pregnancy, has practically dispelled the thought that each pregnancy of a syphilitic woman requires treatment. Several series of patients adequately treated for syphilis have been permitted to go through pregnancy without additional treatment, whether they had received metallic chemotherapy or penicillin in the past.[171-173] Over 500 pregnancies were included in one of these groups. The opinion has arisen that, if there has been a proper response, both clinically and serologically, to adequate treatment prior to pregnancy, additional treatment can be withheld. This is thought to be true of both chemotherapy and penicillin treatment, provided that the normal response to treatment is maintained and a careful follow-up study is instituted throughout the pregnancy. In two of these groups, there were autopsy studies of the few stillborn infants, and no evidence of syphilis was demonstrated. A number of other reports are in general agreement that penicillin therapy is superior to all others in the prevention of congenital syphilis.[117, 174-179] The amounts of penicillin recommended were between 2,400,000 and 6,000,000, the average amount being 4,800,000 units. The largest series included 609 pregnancies, among which there was only a 2 per cent failure rate of living syphilitic infants.[175] It is more or less agreed that as little as 2,400,000 units of penicillin will protect the vast majority of syphilitic women from delivering an infected infant, but this amount will obviously not be satisfactory for the cure of early syphilis in the pregnant woman. Double this amount will be effective for early syphilis in the mother as well as for preventing congenital syphilis, regardless of the duration of pregnancy. In several groups there were high percentages of infants born with positive serologic tests for syphilis, but the serologic titers dropped steadily and became normal by the ages of two to six months.[176, 177] No more than the customary percentages of premature infants that occur in nonsyphilitic women were observed in any of these groups of pregnant syphilitic patients. In one series x-ray studies of 54 infants were reported and 12 of these revealed lesions compatible with healing stages of osseous syphilis.[176] The obvious inference is that these fetuses had been infected by the mother but were cured of their syphilis by the prenatal therapy. In a series of early infectious syphilis in pregnant women, many of whom were treated during the last few weeks before delivery, there were 6 cases of premature labor, which started up during the penicillin therapy.[178] A large group of pregnant women with early latent syphilis, gathered from several clinics, were found to have syphilitic infants in 3.5 per cent of births.[179]

The type of penicillin used appeared to be of little consequence. In several groups, the repository types of penicillin had been employed, with satisfactory effect.[117, 174, 177] Combined therapy has also been used, incorporating repository penicillin twice weekly for six weeks with twelve injections of bismuth.[117]

A study of the factors responsible for the transmission of congenital syphilis is of interest.[180] The records of 77 women who delivered syphilitic infants made up the material of this report. About a fourth of these patients had had negative serologic tests for syphilis and had received no treatment during pregnancy. Many of them may have been in the incubation period of the disease at the time of the negative test, or they may have acquired an infection at a later date in pregnancy. This emphasizes the value of repeating the blood serologic tests in the late months of pregnancy to avoid the disaster of a fresh infection passing unnoticed. The remarkable effectiveness of penicillin in the last weeks of pregnancy would save these women from producing an infected infant.

Congenital Syphilis

It has been well known for many years that the offspring of syphilitic mothers may carry over syphilitic reagin from the fetal circulation, which does not mean that the infant has syphilis. The blood serologic test for syphilis is therefore not reliable in the absence of clinical evidence of congenital syphilis, unless the reagin titer is steadily rising for a period of two months or longer. Since penicillin therapy has come into general usage, it appears that the false-positive serologic titer for

syphilis in newborn infants may persist for longer periods, perhaps up to six months.[176, 177] The effectiveness of penicillin therapy, even in early syphilis that is not treated until the last weeks of pregnancy, has thus brought about another cause for positive serologic tests for syphilis in the newborn infant. It seems highly probable that this false-positive reaction of the infants is not properly termed "false" but is evidence of a treated syphilitic infection contracted and cured in utero.[176, 181] If these possibilities are accepted, the so-called false-positive serologic reaction of the newborn infant has a dual cause. A false-negative reaction can also occur in the newborn. This was reported in 1 per cent of a series of 470 infants of treated syphilitic mothers examined within the first three months of life for serologic, clinical and roentgenologic evidence of syphilis.[181] The so-called false-positive reaction in newborn infants presents one of the most valuable situations for the serial performance of quantitative serologic tests for syphilis.

Statistics published by the United States Public Health Service regarding cases of congenital syphilis reported by state health departments for the continental United States from the years 1941 through 1949 reveal a slow but steady decrease in the amount of congenital syphilis until 1948.[12, 182] In that year, there was a distinct rise, and again in 1949 a further increase occurred. When these figures are broken down into racial components, it is seen that the amount of congenital syphilis in the white race has continued to decrease during the last two years, whereas among the colored population there has been a pronounced increase of congenital syphilis. These figures are not at all in keeping with the claimed reduction in the over-all incidence of syphilis, particularly new infections, or with the remarkable effectiveness of penicillin therapy for syphilis in pregnancy. It is not known whether there is actually an increase in the occurrence of congenital syphilis or if improved case-finding methods have offset a possible decrease in incidence. It is known, however, that in the past eleven years, there has been a continuous decrease in the infant mortality rate from syphilis, which continued at least into 1948.[183] It is further pointed out that only a fifth of the congenital syphilis reported is found in infants under one year of age, the other four fifths being discovered in older children. Most cases are not discovered until the patients reach the elementary school or high school.

The great bulk of this congenital syphilis could have been discovered early. The fact that it is not may be due to failure to examine all the children of infected women. Perhaps too much emphasis has been placed on primary and secondary syphilis in recent years. The tracing of contacts of infectious syphilis probably has not been carried into the study of the family. Only the younger infants of mothers with primary or secondary syphilis could possibly have a congenital infection from this early disease in the mother. Women with latent syphilis, however, may also give birth to congenitally infected children, and many of these may have escaped detection. This situation again illustrates the advisability of a second blood test late in pregnancy. A positive serologic test for syphilis in a pregnant woman constitutes a medical emergency, and no time should be lost in obtaining adequate diagnosis and treatment. If it is a physical impossibility for the pregnant woman to have a prenatal blood test, a serologic examination should at least be done as soon as possible after delivery. A certain amount of congenital syphilis would then at least be detected early when treatment should be more successful.

The possibility of asexual syphilis in children should not be overlooked. A series of 20 cases, with the average age below five years, has been reported.[184] Overcrowded home conditions and lack of education in hygienic matters appeared to be conducive to the acquisition of syphilis in children.

Treatment

There is ample evidence that penicillin is effective in early congenital syphilis, but the degree of success appears to depend more upon the age and physical status of the infant than upon the penicillin dosage. Early in the application of penicillin therapy to syphilitic infants, it was discovered that a total dosage of 100,000 units per kilogram of body weight was probably an optimal amount.[175] The cure rate was estimated at about 75 per cent. Injections were advised at three-hour intervals, to be continued over a fifteen-day period. Only in the treatment of interstitial keratitis did penicillin seem no more effective than metal chemotherapy. Further reports have been confirmatory.[185, 186] If the infant is debilitated, half the customary dosage should be used for the first day or two. Retreatment should be considered in six months if the serologic titer remains high or relapse occurs, and double the original dose may be used at that time. A third course may be required in some children, and combined penicillin-fever therapy should be considered under these circumstances.[185] Most observers have found that the incidence of satisfactory results approaches 100 per cent if treatment is started before the age of three months, with doses approximately 100,000 units per kilogram of body weight, but as much as 440,000 units per kilogram have been used.[187] These authors also employed penicillin by mouth in a small number of infants. They likewise reached the conclusion that the age at the start of treatment is the determining factor in results obtained, rather than the dose or manner of administration of penicillin. Repository penicillin has been used satisfactorily with a dose of 300,000 units every other day, after initial hospitalization for study and preliminary

smaller doses of crystalline penicillin in aqueous solution.[188] Morgan[188] believes that in the older child, penicillin in massive doses (10,000,000 units) should be followed at a later date by arsenic and heavy-metal therapy if there is not a satisfactory serologic response. Interstitial keratitis was discussed above under the conditions grouped together as ocular syphilis.

Treatment Reactions

So little therapy other than penicillin has been used in the treatment of syphilis during the recent past, that only penicillin reactions are considered in this review.

Herxheimer Reactions

An interesting study of biopsy specimens from 21 patients revealed a close correlation of the clinical and morphologic aspects of the Herxheimer reaction.[189] Primary, secondary and tertiary syphilides exhibited a definite sequence in the morphologic alteration. There was first a marked congestion of the capillaries and small blood vessels; later they were crowded with neutrophilic polymorphonuclear leukocytes. These changes, which were sharply confined to the syphilitic lesions, appeared within four hours of treatment and subsided within eighteen hours. It was estimated that careful observation of patients undergoing initial treatment for early syphilis will reveal a Herxheimer reaction in more than 50 per cent of the cases. The incidence of Herxheimer reactions in a group of 939 patients with early syphilis treated with penicillin, gathered from co-operating clinics, was 41 per cent.[190] There was no significant race or sex difference or any variation with the type of early syphilis. There appeared to be no definite trend in relation to dosage, which varied from 10,000 to 120,000 units of penicillin per kilogram of body weight. No febrile reactions were observed when doses of less than 10 units per kilogram were given. The Herxheimer reaction had no influence on the rate of disappearance of spirochetes from syphilitic lesions. The mechanism of this reaction in early syphilis is not known. It has been hypothesized that the reaction is due to the sudden destruction of large numbers of spirochetes, but there is no conclusive evidence to justify this theory. Since the Herxheimer reaction occurs in only about half the patients with early syphilis who receive penicillin, it is of doubtful value as an aid to the diagnosis of syphilis. The report of 2 patients with late syphilis who died shortly after the institution of penicillin therapy emphasizes the possibility of catastrophe in late stages of the disease.[191] The first of the patients here reported, with a proved gumma of the brain, died suddenly and unexpectedly fourteen hours after the initial injection of penicillin. Collateral evidence supported the diagnosis of a Herxheimer reaction, and it seemed certain that death occurred as a direct result. In the second patient there was rupture of an aneurysm forty-nine hours after the institution of penicillin therapy, and the evidence in favor of a fatal Herxheimer reaction was suggestive. Serious reactions have been few, considering the many thousands of patients who have been treated with penicillin.

In a series of 349 patients with neurosyphilis who were treated with penicillin, the total incidence of Herxheimer reactions was found to be 34 per cent.[192] The diagnostic type of neurosyphilis and the degree of abnormalities in the cerebrospinal fluid were found definitely to influence the incidence of reactions. Febrile reactions occurred in approximately 75 per cent of the patients with dementia paralytica as compared with only 25 per cent of those with all other types of neurosyphilis. The incidence was higher in patients in whom the white-cell count and total protein content were abnormal and in those who had strongly positive reactions to complement-fixation tests on the cerebrospinal fluid. There was no significant difference in the incidence of reactions between patients who had received recent metal chemotherapy and those previously untreated. Trial therapy with small initial doses of penicillin (20 units per kilogram of body weight) seemed to indicate that Herxheimer's reaction could not be avoided by the administration of repeated small doses of penicillin.

A study of the reactions to penicillin in the treatment of syphilis in pregnancy indicated that the reactions were generally mild and consisted primarily of urticaria and febrile Herxheimer reactions.[193] In 2 cases it was believed that a serious reaction in the form of a placental or fetal Herxheimer phenomenon occurred, resulting in premature labor and the delivery of a stillborn fetus. In both cases fetal movements and fetal heart sounds were present before treatment was started but ceased within twenty-four hours of the institution of penicillin therapy. It is of interest that none of the authors cited above in the section on syphilis in pregnancy reported a similar situation.

In congenital syphilis treated with penicillin, febrile elevation or definite Herxheimer reactions have been reported in a sixth to a third of two groups of patients.[188, 194] The occurrence of febrile Herxheimer reactions had little or no bearing on the serologic outcome.

It is apparent from these reports that the Herxheimer reaction has not been of vital consequence in many cases, considering the volume of penicillin therapy employed in recent years. Nevertheless, there are numerous situations, particularly in late syphilis, in which such a reaction could entail a fatal result. Certainly, more study is required for further elucidation of possible means of circumventing the Herxheimer phenomenon.

Penicillin Sensitivity

When penicillin first came into use, it was thought to be almost entirely incapable of causing reactions of any sort. As this antibiotic became more widely employed, the variety of reactions gradually accumulated to considerable proportions. Fortunately, these have nearly all been mild, but they may at times be rather distressing. The problems of managing patients who manifest reactions to this drug assume greater practical importance as its use increases. A study of the clinical problems of penicillin sensitivity revealed that 5.4 per cent of 265 adults who had never had penicillin reacted "spontaneously" to a forty-eight-hour cutaneous penicillin test.[195] Of 65 children, none reacted positively. Among 130 patients who received penicillin, 32 had cutaneous eruptions, 25 of which were of the urticarial serum-sickness type and 7 of the erythematovesicular type. Eruptions developed in 34.2 per cent of men but in only 8.3 per cent of women. Seventeen of the 32 patients who developed cutaneous eruptions reacted positively to the cutaneous penicillin test. A schedule of dosage for subcutaneous desensitization is given in the article. A decision to readminister penicillin should be guided in part by the cutaneous test and by the intensity of the previous eruption. This work was not done in patients with syphilis, but it may be of value in the occasional syphilitic patient who should receive penicillin and is prevented from having it by previous sensitization. Other forms of antisyphilitic therapy could usually be employed but might be either ineffective or contraindicated. Another discussion of the same problem subdivides the reactions to penicillin into those of hypersensitivity, toxicity, reactions from faulty technic of administration and miscellaneous situations, including the Herxheimer reaction.[196] This is a complex classification but nevertheless clearly portrays the wide variety of untoward reactions that may be observed in penicillin therapy. Twenty-four subdivisions are included, with descriptions of the more important features of these reactions and a discussion of testing procedures.

The occurrence of the delayed serum-sickness-like reactions to penicillin has been reported as 1.7 per cent in a series of 181 patients treated at a United States Navy dispensary.[197] A mild leukocytosis was usually present, but no eosinophilia. A low-grade fever, arthralgia and localized edema accompanied the reactions. A bizarre complication of the severe urticarial reaction accompanied by arthralgia has been reported in the form of a toxic psychosis.[198] The authors suggest that, along with the severe generalized urticaria, the patient may have developed an edematous lesion of the brain, which in turn was responsible for the mental confusion. Exfoliative dermatitis is one of the more severe cutaneous reactions and has been reported in a hemorrhagic, gangrenous form.[199]

A distressing, but usually not serious, local reaction is occasionally observed after penicillin injection in the form of so-called "pseudocellulitis."[200] This is characterized by the rapid appearance of severe tenderness at the site of injection. There may be generalized malaise and a moderate elevation of body temperature. The skin over this area assumes a somewhat erysipeloid appearance. This reaction usually recedes spontaneously in a week or ten days, but a small, tender nodule may remain for a protracted period. It is helped by ice packs and aggravated by heat. This reaction should not be confused with an inflammatory lesion caused by infection.

The type of penicillin preparation administered and the size of the doses appear to have some influence on the incidence of reactions.[201] Among 598 patients receiving crystalline penicillin in aqueous solution in moderate dosage, 1.2 per cent manifested hypersensitivity to penicillin. A second group of 557 patients treated with penicillin in oil and beeswax reacted at the rate of 2.7 per cent. A third and smaller series of 148 patients were given procaine penicillin in oil, and the reaction rate was 1.4 per cent. With exceedingly high doses of aqueous penicillin, the incidence of reactions increased to 7.8 per cent. Allergic reactions were more frequent when the penicillin was continued for a longer period. Local reactions were more frequent and more severe when penicillin in oil and wax was injected. It has been stated that spontaneous desensitization to penicillin may occur.[202]

Despite its relatively nontoxic properties penicillin is a potent sensitizing agent and should be regarded with respect. The indiscriminate use of this drug for minor disturbances by physicians and the commercialization for over-the-counter sales by pharmaceutical manufacturers are doubtless responsible for many cases of unnecessary sensitization that jeopardizes the patient who may be in dire need of future therapy with this valuable antibiotic agent.

Summary

There has now been approximately a seven-year period in which to study the value of penicillin in the treatment of syphilis. It is unquestionably the most effective, convenient and relatively nontoxic therapeutic approach to this disease yet discovered. The conveniently short schedules of treatment have resulted in a far greater percentage of patients who complete their treatment. Procaine penicillin in doses of 4,500,000 to 6,000,000 units administered in about fifteen days appears to be the optimal amount required to cure 80 to 90 per cent of early infectious or early latent syphilis. Higher cure rates have been obtained in some groups, but the most desirable treatment plans are yet to be

determined. Late benign syphilis will generally respond to the same amount, but late visceral disease is not so responsive. Neurosyphilis requires from 9,000,000 to 12,000,000 units in about three weeks, and the more severe parenchymatous forms are frequently in need of fever therapy in conjunction with penicillin. The schizophrenic type of dementia paralytica is the most difficult of all forms of syphilis to control. A satisfactory treatment schedule for interstitial keratitis is still to be determined. The unborn child of a pregnant syphilitic woman can almost invariably be protected from the disease by 4,000,000 or 5,000,000 units of penicillin. Retreatment in subsequent pregnancies is seldom necessary if the clinical and serologic response of the mother has been satisfactorily maintained. The determining factor in congenital syphilitic disease is early treatment, preferably before the age of three months, when it is generally modified only by the physical condition of the infant.

The use of semiweekly treatment schedules appears to have considerable promise. An outstanding attempt at preventive medicine is to be seen in the experimentation with "abortive" treatment for the contacts of patients with infectious syphilis.

The clinical problems related to the serology of syphilis, the biologic false-positive serologic reaction and the question of reinfection versus relapse continue to be enigmatic. The final interpretation of these situations rests on clinical judgment and experience, without which the greatest feats of the laboratory may be fruitless.

The lack of understanding of the features of immunity in syphilis has been a great hindrance. The discovery of an immobilizing antibody in the serums of syphilitic animals and human beings that is believed to kill *Treponema pallidum* is encouraging. This antibody is not the same as the Wassermann reagin.

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

BENJAMIN CASTLEMAN, M.D., *Associate Editor*

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CASE 36501

PRESENTATION OF CASE

A twelve-year-old girl was admitted to the hospital because of weakness, diarrhea and loss of weight.

Ten years prior to admission the child was admitted to another hospital with an elevated temperature, abdominal cramps and diarrhea with melena. Physical examination showed pallor and malnutrition. Blood agglutinations tests for typhoid, paratyphoid and undulant fever were negative. A gastrointestinal series, barium-enema study and proctoscopy were also negative. The diarrhea and fever subsided. Four months later there was a recurrence of blood in the stools, which were unformed, and she had two or three bowel movements a day. Readmission failed to reveal any further pertinent physical signs. The hemoglobin was 70 per cent, and the red-cell count 4,500,000. The bleeding and clotting times were normal. The stools were persistently guaiac positive, and a laparotomy was performed later that year, with negative findings. Nine years before entry she was admitted to another hospital again. Attacks of rectal bleeding had occurred periodically and were accompanied by fever, loose stools and vomiting. The stools between attacks appeared normal. The stools were negative for ova or parasites. Tuberculin tests were negative in dilutions down to 1:100. An x-ray film of the chest was normal, and a barium-enema examination revealed numerous lesions characteristic of ulcerative colitis. Subsequently, she had been hospitalized five times for periods of two to three weeks. She was never symptom free, but there had been fairly marked fluctuations during the course of the illness. The last hospitalization was ten months prior to admission here, and for six months thereafter she was fairly well. She had two loose bowel movements daily without visible blood in the stool. Her appetite was good, and she was active. However over the five months prior to admission she became increasingly lethargic, her appetite lessened, and she lost 2 pounds in weight. There was no change in frequency, type or amount of stools passed.

The child had been breast fed for four months and then changed to a whole-milk formula. No feeding problems or bowel difficulty in the neonatal period or early infancy occurred and she developed normally.

On physical examination almost the entire abdomen was filled by a large, firm, nontender mass continuous with liver dullness. A definite edge that descended with inspiration was felt. The edge extended almost to the iliac crest on both sides. The mass felt somewhat nodular to palpation. A firm, nontender mass believed to be the spleen was palpated four fingerbreadths below the left costal margin. Examination of the head, neck, chest, heart, extremities and rectum was normal.

The temperature was 98°F., the pulse 122, and the respirations 26. The blood pressure was 120 systolic, 80 diastolic.

Urinalysis was normal. Examination of the blood showed a red-cell count of 3,120,000, with a hemoglobin of 5.8 gm., and a white-cell count of 6900, with a normal differential. The total protein was 6.92 gm., the albumin 4.59 gm., the globulin 2.33 gm., the nonprotein nitrogen 18 mg., and the alkaline phosphatase 7.9 units per 100 cc.; the sodium was 135.6 milliequiv., the chloride 106 milliequiv., the potassium 5.0 milliequiv. and the carbon dioxide 23.4 milliequiv. per liter. The prothrombin time was normal, the cephalin flocculation ++ in twenty-four hours and +++ in forty-eight hours, the thymol turbidity 2.5 units, the thymol flocculation negative, and the van den Bergh reaction 0.2 mg. direct and 0.3 mg. total per 100 cc. The Congo-red test showed 81 per cent retention in the serum after one hour, and the bromsulfalein test 10 per cent retention after forty-five minutes. The stools on numerous examinations were brown and fluid and contained mucus. An occasional stool was guaiac positive. Cultures were negative for pathogens. Bone-marrow examination was not remarkable. Sigmoidoscopic examination showed the mucosa throughout to be granular, with streaks of white. The vascular pattern was not visible. Mucus was somewhat increased, but there was no bleeding when the bowel was wiped. The bowel was spastic but flexible throughout. The sigmoidoscope was passed its full length of 15 cm. to several centimeters within the sigmoid.

An x-ray film of the abdomen showed a very large liver extending down below the iliac crest. The spleen was twice the normal size. There was a rather homogeneous appearance to the upper abdomen, suggesting the possibility of some peritoneal

fluid. At barium-enema examination the barium filled the colon to the cecum quickly, demonstrating a markedly narrowed, shortened and distorted colon. No normal mucosa was seen in any region. Multiple areas of small filling defects suggested the presence of pseudopolyposis. In the distal transverse colon there was a 5-cm. segment of constant narrowing with shelf formation at either end and with ulcerations in the narrowed portion (Fig. 1).

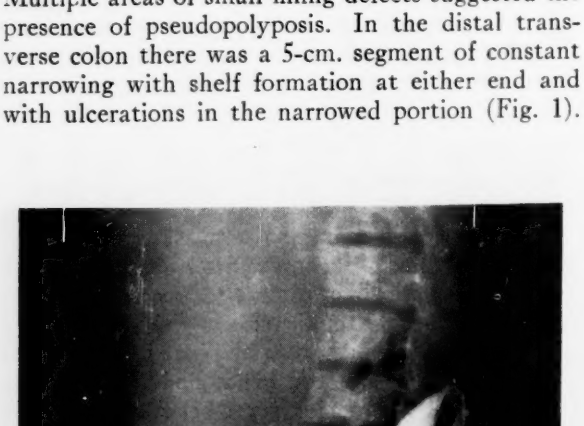

FIGURE 1. *Barium-Enema Examination. Note enlarged liver pushing down transverse colon. Arrows point to shelf formation.*

On the fourth hospital day an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR. JOSEPH GARLAND*: To recapitulate, this child for ten of her twelve years had disease of the gastrointestinal tract. What started it I do not know, and even with the x-ray and sigmoidoscopic findings if I predict that she had an ulcerative colitis, such is the nature of the Case Records of the Massachusetts General Hospital that I shall probably be wrong. However, there seems to be very little else that I can make for an initial diagnosis. This girl started at the age of two to have diarrhea and loose stools, with pain and blood. The first gastrointestinal and proctoscopic examinations were negative. The symptoms were intermittent, and because of the recurrence of blood four months after the onset of the disease a laparotomy was performed. Exactly what was in mind when the laparotomy was performed, I am not sure. Perhaps the physicians were looking for some congenital defect or something that was outside the range of my present information. Certainly, a regional enteritis is very uncommon at this age, and I hardly think it need be considered. This laparotomy must have been performed as a diagnostic procedure, apparently with no idea at that time that an ileostomy might be necessary. After that the history went on about as before. She had these attacks of bleeding, with fever and with loose stools, and later in the same year, presumably before she was three years old, she had a barium-enema examination showing some slight spasticity of the descending colon and numerous lesions characteristic of ulcerative colitis. We have to accept that as our official diagnosis, and from that period on the course was reasonably characteristic of an advance of ulcerative colitis. Finally, the patient came into the hospital, not entirely because of weakness, diarrhea and loss of weight of five months' duration, but because of the ten-year history of diarrhea with blood and mucus, loss of weight and generally poor nutrition, which reached a critical point apparently during the five months prior to admission so that she was definitely more ill than she had been. We now find an emaciated young girl with large masses in the abdomen, presumably a liver and a spleen. She had an anemia, probably a secondary anemia, since the blood smear was not abnormal — just a low hemoglobin and a diminished red-cell count. The total protein was approximately normal with a normal albumin-globulin ratio. The nonprotein nitrogen was a low normal of 18 mg. per 100 cc. The cephalin-flocculation test was high and did indicate something wrong with the liver. Thymol turbidity also showed presumably hepatic damage. The van den Bergh reaction was approximately normal. The Congo-red test was normal. The bromsulfalein test showed increased retention, indicating again something wrong with the liver.

At this point it might be wise to look at the x-ray films.

DR. STANLEY M. WYMAN: As recorded in the protocol the shadow of the liver is distinctly enlarged, extending down to the iliac crest and across the midline. The spleen, although it cannot be well outlined, seems to be somewhat enlarged but to a lesser degree. The barium-enema examination shows gross narrowing and irregularity with fine ulceration. The margins of this mass appear quite well defined and suggest shelf formation (Fig. 1).

DR. GARLAND: I do not know whether or not this narrowing is significant of anything particular. Out of ignorance I will assume that the whole picture could be caused by a chronic ulcerative colitis, and I shall make that an original diagnosis.

Since particularly with children we try to go on the theory of the paucity of hypotheses and try

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not to include too many unrelated diseases, I should presume that the great enlargement of the liver and spleen depended on the original colitis. It is known that hepatic cirrhosis can be secondary to a chronic infectious disease, particularly of the gastrointestinal tract. A patient who has been sick as long as this child had, despite her age, could, I presume, have a secondary amyloidosis, which also may occur following a chronic gastrointestinal infection. The Congo-red test was not consistent with amyloidosis, but whether or not that rules out amyloidosis I do not know. I do not know enough about the value of that particular test. I do not think I need to talk about Banti's disease. I think it is enough to say that there was hepatic cirrhosis secondary to the chronic infection.

The patient had an operation performed after she had been in the hospital four days. Of course one is intrigued by the reason for the operation. Was it a laparotomy to take a peek to see what was wrong inside, or was it to do something therapeutic? Was the spleen removed because she had Banti's disease? I do not believe so. Was an ileostomy done with expectation that some part of the colon could be rescued? I am sure I do not know. Also, one wonders, if this was a simple ulcerative colitis at the start, why she should have pursued a course of this duration without having had an ileostomy much earlier than this. I think with that, Dr. Mallory, I shall have to sit down and rely on the experts to tell us what it really was.

Dr. Alfred E. Kranes: In adults one of the more frequent complications of long-standing ulcerative colitis is carcinoma of the colon. I wonder, in view of the constriction found by Dr. Wyman and the enormously enlarged liver, whether that should not be considered. Does that often occur in children?

Dr. Garland: It certainly can occur in children, but I have not run into such a thing. The liver also was nodular. With cirrhosis at certain stages it is nodular.

Dr. Kranes: One thing that disturbs me about making that diagnosis is the enlargement of the spleen, which is rather infrequent. What do you think about the constriction, Dr. Wyman?

Dr. Wyman: We thought it was carcinoma of the colon.

Dr. Tracy B. Mallory: Dr. French, I believe you saw this patient in consultation.

Dr. Arthur French: I can answer Dr. Garland's question about the operation. I am afraid we misled him because we do not very often do liver biopsies on children. The operation was a liver biopsy. We were impressed by the great size and firmness of the liver so that we did not think too much of cirrhosis in this patient. The Radiology Department believed very strongly that it was a carcinoma, but, as Dr. Kranes has suggested, we were impressed by the fact that the spleen was definitely separated from the liver. We did think tumor was present and were more inclined to a lymphoma than a carcinoma. We did a liver biopsy, hoping that we might find a lymphoma that might possibly be radiosensitive.

Clinical Diagnosis

?Lymphoma, ?metastatic carcinoma of liver.

Dr. Garland's Diagnoses

Ulcerative colitis.
Hepatic cirrhosis, secondary to colitis.

Anatomical Diagnoses

Metastatic carcinoma of liver.
(*Ulcerative colitis with superimposed carcinoma in a twelve-year-old girl.*)

Pathological Discussion

Dr. Mallory: I think as Dr. Kranes suggested this can be tied into one. One of the logical sequelae of ulcerative colitis is the development of carcinoma of the bowel. It occurs in only a limited number of cases but in a sufficiently high percentage to have unquestionably a causal relation. The operation was essentially a punch biopsy of the liver. I am constantly surprised at how frequently in a little cylinder of liver tissue removed through a needle one can pick up tumor cells or fragments of metastatic tumor. That was so in the case under discussion. There were multiple foci of poorly differentiated carcinoma in the liver — in a few areas just a little suggestive of gland formation that is consistent with metastases from a primary tumor of the bowel. This was, I think, the first case of carcinoma developing in ulcerative colitis that we have seen in childhood; we have seen several in adults. In a certain number of cases of ulcerative colitis a marked hyperplasia of the mucous membrane of the bowel develops that is ordinarily spoken of as pseudopolyposis, and I believe that was suggested by the Radiology Department in this case. Sometimes it is very difficult to decide whether it is a pseudopolyposis or a true polyposis. Eventually, in either case, carcinoma may develop. Carcinoma of the large bowel in childhood is most often seen in cases of congenital polyposis but occasionally in a case like this of ulcerative colitis of long duration.

Dr. Kranes: Is the patient still alive?

Dr. Mallory: I do not think we have a follow-up report. The patient was given a trial of nitrogen mustard therapy and was discharged to another hospital, presumably to die.

A Physician: Was the enlargement of the liver due entirely to metastatic carcinoma, or was there amyloidosis?

Dr. Mallory: There was no amyloidosis. The liver appeared entirely normal except for the carcinoma.

DR. KRANES: What was the explanation of the splenomegaly?

DR. MALLORY: We have not explained that. I am willing to raise the question whether there was a splenomegaly or not, but I cannot say there was not. A metastatic nodule in the left lobe certainly could give the same appearance.

CASE 36502

PRESENTATION OF CASE

A sixty-three-year-old woman was admitted to the hospital complaining of vomiting of blood.

Three years prior to admission there had been an episode of rectal bleeding and hematemesis. An x-ray film of the stomach done at another hospital showed no abnormality. She received treatment for rectal polyps, the symptoms cleared, and she was perfectly well until six months prior to admission. Beginning then she began to complain of epigastric burning pain and indigestion with gas. This was not related to, or relieved by, food. On rare occasions she vomited, with relief of the pain. Neither blood in the vomitus nor tarry stools were noted at this time. Three days prior to admission she passed a black stool and vomited a small amount of brownish-red material. She was admitted to another hospital, where she received a blood transfusion. She continued to have tarry stools, vomited blood and so was transferred to this hospital.

There had been no previous history of gastrointestinal disturbance. The bowel habits were regular, and there was no recent change. For some years there had been mild dyspnea on exertion and swelling of the ankles on standing. Thirty years before entry a lower abdominal operation, type unknown, had been performed. The menopause occurred at the age of fifty, with no vaginal bleeding since. She did not drink wine or liquor.

On physical examination the lungs and heart were normal. The abdomen was obese, soft and nontender. There were no palpable masses or organs. There was a small cervical polyp. Rectal examination revealed a soft, tarry-appearing stool in the rectum.

The temperature was 101°F., the pulse 120, and the respirations 25. The blood pressure was 98 systolic, 60 diastolic.

Urinalysis was normal. Examination of the blood disclosed a hemoglobin of 7.8 gm. The nonprotein nitrogen was 52 mg., and the total protein 4.9 gm. per 100 cc., and the chloride 96 milliequiv. per liter. The prothrombin time and the bleeding time were normal.

Following admission a 1000-cc. blood transfusion was given, and the blood pressure rose to 120 systolic, 70 diastolic. This was not sustained, and five hours later the blood pressure was 86 systolic, 50 diastolic, and the pulse 96. A barium swallow with the patient in the supine position demonstrated a probable hiatus hernia, a normal stomach and nothing definitely abnormal in the duodenum, although it did not seem to fill well. Following this procedure she seemed to improve somewhat, and on the second hospital day the blood pressure was stabilized at 110 systolic, 90 diastolic. The hemoglobin was 10 gm. The temperature was 101°F. and the pulse 100 to 110. Two gastric aspirations performed during this day yielded normal stomach secretions, which were guaiac negative. Proctoscopic examination revealed a soft, irregular sessile polyp on the left posterior wall of the rectum with a granulating oozing surface, but no major bleeding. It was located 2 inches proximal to the sphincter and was flat and easily movable. The proctoscope was passed to 10 inches, at which point a dark-black clot was seen. On barium enema the mixture readily entered the rectum and reached the cecum without delay. There was reflux into a normal-appearing terminal ileum.

On the morning of the third hospital day the hemoglobin was 9 gm. The patient vomited undigested pure clot and passed tarry stools, which were guaiac positive. In spite of transfusions the hemoglobin dropped to 8.6 gm. late in the afternoon, and to 6.0 gm. during the subsequent night. The blood pressure dropped to 85 systolic, 65 diastolic.

Gastric aspiration on the morning of the fourth hospital day yielded at first only mucus, but later a small amount of bright-red blood was aspirated. Later that morning an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR. EARLE M. CHAPMAN*: This case really should be discussed by a surgeon rather than an internist. When Dr. Castleman asked me to discuss it, he told me quite frankly that he could not

*Associate physician, Massachusetts General Hospital.

find a surgeon because they were all attending the meetings of the American College of Surgeons.

May I see the x-ray films?

DR. STANLEY M. WYMAN: These films of this heavy woman are somewhat underpenetrated. The hernia is readily visible; the stomach itself seems to be grossly normal. I can see no filling defects.

DR. CHAPMAN: Can you see any varices? It would be helpful if you could.

DR. WYMAN: I do not think that she had varices. The duodenum is very well shown on these spot films, and its contour appears normal.

DR. CHAPMAN: Can you see the second portion?

DR. WYMAN: It is very easily seen and appears normal.

DR. CHAPMAN: What about the third portion?

DR. WYMAN: I can see only a very small portion of it.

DR. CHAPMAN: I am presented with a challenge regarding the diagnostic possibilities in a patient aged sixty-three who was quite well except for epigastric pain of some six months' duration and who suddenly began to lose great quantities of blood both by rectum and by mouth. The studies resolve here into the fact that the ulcerating lesion that lay within the gastrointestinal tract could not be identified or localized. It is true that a rectal polyp was discovered, but that, I think, probably was incidental. I cannot believe that the polyp was part of a generalized disease and that the patient also had polyposis at this higher level.

There are other things to consider, of course. The two commonest sources of bleeding are esophageal varices and varices in the neck of the stomach from cirrhosis of the liver, but there was nothing that I can see to support either diagnosis. Varices could not be seen in the esophagus, which was well outlined in the x-ray films. There is only one thing in the laboratory data that makes me a little suspicious of that. The total protein was 4.9 gm. per 100 cc. For an acute bleeding episode I cannot believe the loss of protein in proportion to the blood would be as great as this. It suggests that the patient had been losing serum protein from the blood before the acute episode. However, I think the Radiology Department has excluded both these possibilities.

The other things I have to consider are numerous. I do not believe I am dealing with the condition that Hale-White,* the great English clinician, first described called "gastrostaxia," in which diffuse oozing through the stomach and upper digestive tract occurs with an inflammatory process that is so diffuse that it cannot be diagnosed on x-ray examination. On pathological examination a raw, reddened mucosa is seen. It is thought that by a sort of capillary diapedesis the blood oozes out, causing a massive hemorrhage. Nor can I believe that this patient had a disease within the lower small intestine, such as Meckel's diverticulum with ulceration, which tends to happen more often in the younger age group. The barium-enema examination was reported as negative; thus, there must have been an ulcerative process somewhere near the head of the pancreas in the second or third portion of the duodenum, and the epigastric burning pain was the symptom that pointed to this lesion of some four or five months' duration. If so it would have been near the ampulla of Vater, and would not have obstructed the ampulla or produced jaundice. From the evidence, all I can say is that she had an ulcerative bleeding lesion in the upper gastrointestinal tract most likely near the ampulla of Vater and perhaps in the second portion of the duodenum that is not well shown on the x-ray films.

Other rare conditions such as leiomyosarcoma of the jejunal junction and other sites along the course of the intestines should be considered. It is also possible that this rectal polyp was accompanied by polyps higher up. I am unable to make another diagnosis from the evidence at hand. I wonder what the surgeon found?

DR. BENJAMIN CASTLEMAN: Would you like to comment further about the ulcerating lesion in the second portion that you think she had. Was it benign or malignant?

DR. CHAPMAN: I suspect that, at sixty-three years of age, it was probably malignant. I should have commented about the operation thirty years before admission. With obstructive symptoms one thinks of some interference with blood supply and damage to the bowel from the old operation, but I do not believe that was present. I think an ulcerating lesion in the second portion of the duodenum near the ampulla is my best bet, and in a patient at the age of sixty-three I think it was probably malignant.

*Hale-White. Cited by Osler, W. *Principles and Practice of Medicine.* Revised by H. A. Christian. Fourteenth edition. 1475 pp. New York: D. Appleton-Century Co., 1942. P. 673.

Dr. Alfred Kranes: I wonder why Dr.Chapman did not discuss the possibility of bleeding from a diaphragmatic hernia.

Dr. Chapman: I voted against that because the aspirations from the stomach were clear and there was nothing to indicate that the blood was coming from either within the stomach or just above it. Only the last aspiration showed a little bright-red blood, which may well have been due to trauma.

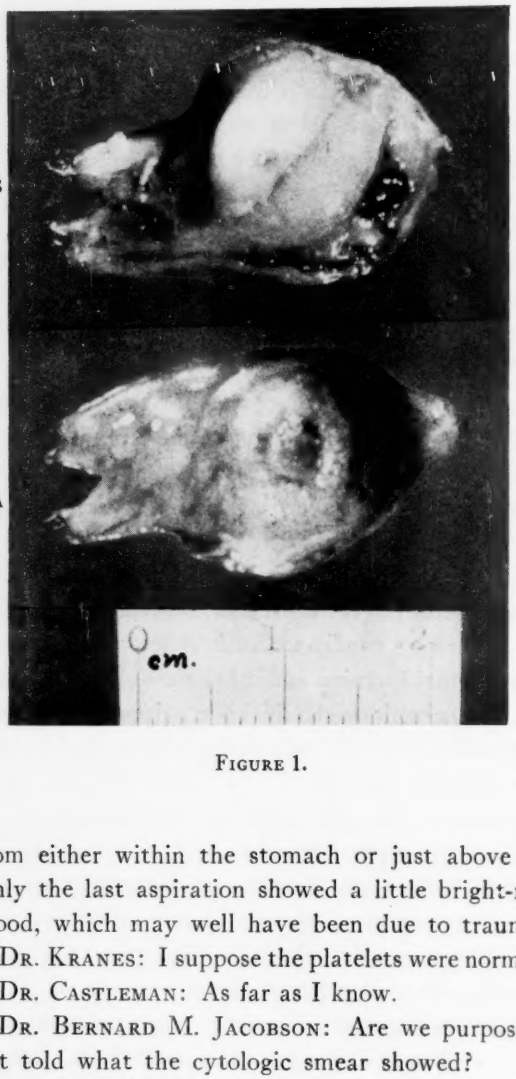

Figure 1.

Dr. Kranes: I suppose the platelets were normal.

Dr. Castleman: As far as I know.

Dr. Bernard M. Jacobson: Are we purposely not told what the cytologic smear showed?

Dr. Castleman: None was done.

Clinical Diagnosis

Upper gastrointestinal bleeding of unknown origin.

Dr. Chapman's Diagnosis

Ulcerating lesion, malignant, second portion of duodenum.

Anatomical Diagnosis

Leiomyoma, first portion of duodenum.

Pathological Discussion

Dr. Castleman: At operation the external examination of the stomach was found to be perfectly negative, but in the first portion of the duodenum, in the cap apparently, the surgeon felt a nodule 1 cm. in diameter that he merely excised. On the inside of the specimen the duodenal mucosa was raised over the nodule, and there was a dimple with ulceration in the center (Fig. 1*A*). Cross-section of the nodule revealed a fibrous tumor (Fig. 1*B*), which on microscopical examination proved to be a benign leiomyoma. It was very similar to the submucosal tumors that are usually seen in the stomach producing a central mucosal depression and ulceration.

Dr. Jacobson: What was done at the operation?

Dr. Castleman: Just a local excision of the tumor with the surrounding mucosa. The lesion was high enough in the duodenum so that there was no interference with the biliary-duct system.

Dr. Farahe Maloof: Is there a follow-up report?

Dr. Castleman: The patient has gone home perfectly well. Knowing where the tumor is now, can you see it on the x-ray film, Dr. Wyman?

Dr. Wyman: I am ashamed to say I have seen these films twice and missed the lesion twice. I have a difficult time finding it even when I know it is there. I only find it when I am told there is a lesion that I have to find.

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"PEACE ON EARTH"

THE editors of the *Journal* have conferred long, with classically corrugated brows, on the propriety of publishing this year a Christmas editorial.

The question did not so much concern the desirability of continuing such a custom, for so long pleasantly prevalent throughout the so-called Christian world, as it did the consistency of this expression of good tidings, in a world that is facing such determined opposition to the principles of Christianity. For sinister groups with whom rests much of the initiative for what is transpiring between nations have been in the ascendant, destroying liberty in the name of freedom and shedding darkness in the name of light. They are the villains of the pageant and they never hang up their stockings on Christmas Eve, unless it happens to fall on a washday.

To counter this threat there has so far been evident considerable indecision and vacillation with a tendency to appeasement, international and party jealousies, more than a little evidence of treasonable practices, hysterical fear on the part of many, and thin lines of soldiers fighting strange enemies in a strange land.

In the western world what appears to be a general devotion to stream-lined materialism exists, coupled with a slap-happy generosity. Things, to a great many people, are apparently more important than ideals. The concern is not whether Santa runs a risk of chimney sweep's cancer, but whether he can get his pack down the flue.

These distressing signs and uncertainties have caused the question again to be raised, and seriously, whether there really is a Santa Claus, or only a balloon made in his image, filled with the usual content of balloons, and whether Christmas has any real meaning aside from its commercial value.

Democracies, however, customarily wear their jackets inside out. It is part of their very nature that they must present their weaknesses to the world; and this, in fact, is one of the elements of their strength. The consternation that strikes their single-purposed, totalitarian adversaries when they discover the hidden layer of resistive strength turns out often to be of incalculable strategic value to the democratic cause.

The late Viscount Bryce, once England's ambassador to this country and author of *The American Commonwealth*, likened democracy to a leaky vessel, ill manned, that somehow manages usually to make its port with decks awash. The absolute state, on the other hand, tightly caulked and with a firmly disciplined crew speeds swiftly on its course, but owing to fundamental faults of navigation usually strikes a hidden rock and goes down.

Beneath the soft surface that sometimes seems to cover democracy, other resources may be discovered. One need not become a pagan, as Wordsworth suggested, to find visions that would make him less forlorn. There is still an underlying integrity in the people. Countless persons are still mindful of their fellow men and given to good works in their behalf. Established religion, conscious of the dangers that beset it, as well as of its indispensability to man's

progress, is determined to carry on its struggle against indifference from within and attack from without. Those principles of Christianity that can be respected by men and women of every belief make Christmas still the day of universal rejoicing over much of the earth.

And so the editors, having made their decision, wish for the readers of the *Journal* continued belief in eventual peace on earth to men of good will!

A REMINDER

THE members of the American Medical Association, for the first time in its history, have this year been asked to pay dues to the organization. This logical requirement for membership has been variously announced and was commented on editorially in the *Journal* on April 6, 1950. Accompanying the bill for these national dues that emanated early in the spring from the offices of the Massachusetts Medical Society, was the announcement that any active member who had failed to pay the assessment by the end of the year should forfeit his membership in the Association.

As the year of grace draws to its close an unpalatable fact must be called to the attention of the fellows of the Massachusetts Medical Society. It is that this society, the oldest and hitherto one of the most active and respected of the state societies, is also one of the most delinquent in meeting this reasonable obligation of the American Medical Association.

The latest report received from the headquarters of the Association on November 24 indicates that dues have so far been collected from over 90 per cent of the membership of several state societies, from an average of 70 per cent of the members of all the societies, and from 57 per cent of the fellows of the Massachusetts Medical Society, giving to this society an unenviable thirty-sixth place among the state organizations.

Some of these defaults are undoubtedly due to a lofty conviction on the part of the delinquent member that his association can do no good and he will have no part of it; the majority probably result from that carelessness in business matters that seems to be a cherished part of the medical heritage. That this should apply particularly to Massachusetts is a matter for the record if not for any self-congratulations.

Those in the latter category surely need only a gentle reminder of their oversight to make them spring to their checkbooks; the first-mentioned group must be made aware of the fact that if they are really interested in improving the standards of their profession and the scope and quality of the service that it can render, they can do so more effectively from within the organization than from outside it.

Both groups must bear in mind that representation in the House of Delegates of the American Medical Association is based on the ratio of one representative to each thousand active members. The Massachusetts Medical Society consequently stands to lose 3 or 4 of its 7 delegates and a proportionate degree of influence in the House if nearly half its membership drops out of the national association.

Never before in the history of the world has a united front on the part of all good citizens been so necessary. Never has a cause been saved by the desertion of its natural supporters.

HOPE FOR THE ALCOHOLIC

NOVEMBER 16, 1950, marked another turning point, indicative of continued enlightened progress, in the administration of the Department of Public Health of the Commonwealth of Massachusetts. On that day, following the lead of Virginia, New Jersey and Pennsylvania, the State became the fourth in the union to set up a special division of alcoholism, thus establishing an attempt at controlling this disease as a part of its general public-health program.

Such a move is particularly appropriate in Massachusetts, for not only has this proud commonwealth the distinction of having established the first state board of health in the country, in 1869, but in the importance of its alcohol problem it ranks fifth among the states. In Massachusetts, in fact, according to a statement of Dr. Vlado A. Getting, commissioner of public health, 1 per cent of the

adult population "has been physically or psychologically damaged by excessive drinking of alcohol."

The immediate plans of the new division envisage a triple attack on the problem, consisting of diagnosis, treatment and rehabilitation of the individual patient; prevention and education; and research in both the medical and public-health aspects of chronic alcoholism. The work of such agencies as Alcoholics Anonymous, committees for education on alcoholism and other interested groups, and presumably the nationally recognized Washingtonian Hospital, will be recognized in the co-operative effort. Already clinics for rehabilitation have been opened under the sponsorship of the Department of Public Health at the Peter Bent Brigham Hospital in Boston and the Quincy City Hospital.

The director of the new division is Dr. John C. Ayres, formerly assistant director of the division of communicable diseases of the Department.

The concept of the role of the State in medicine, enunciated by Henry I. Bowditch* in 1876, has been considerably broadened, and yet in its principles holds as true today as it did then.

> "Hence, preventive medicine [Dr. Bowditch said in the Centennial Discourse on Public Hygiene in America, delivered at Philadelphia] must be undertaken by the State, or we shall hereafter go on as hitherto, with but little success, against what may be preventable diseases.
>
> "Still further I hold it to be true that the study of the prevention of disease is the only branch of medical learning which the State can legitimately undertake. . . ."

To this, of course, may be added the treatment and care of those unable to care for themselves.

In the study and prevention of the disease, alcoholism, and in the care and treatment of those alcoholic patients who are unable properly to care for themselves, it seems that the State has legitimately assumed a problem in preventive medicine and public health.

The limited budget of $40,000 to cover costs until June 30, 1951, seems modest when compared with the estimated annual cost to state governmental agencies of $61,000,000 for incarceration of problem drinkers and the care of their families.

*Emerson, H. Whither Pegasus of public health? *New Eng. J. Med.* 238:679-687, 1948.

TEMPORA ET MORES

It has been decided for various reasons that the proceedings of the Council of the Massachusetts Medical Society and the detailed account of the annual meeting should be published as a special supplement to the *Journal* rather than being incorporated in it as heretofore. This supplement will be sent separately to the fellows of the Society and to any other subscriber who burns with a passionate desire to peruse these simple annals, faithfully transcribed if not always aglow with the pure light of literary merit.

The primary reason for the change has to do with that rare virtue in this age, economy, and has been proposed by the niggardly management of the *Journal* to save the paper, printing and mailing involved in the production and distribution of some 20,000 presumably superfluous copies of this largely documentary material. Costs, as is well known, are rising.

It is believed, also, that this policy will be favored by those distantly located subscribers who might conceivably be less interested in the Report of the Representative on the Professional Advisory Committee Organized by the Division of Vocational Rehabilitation of the State Department of Education for the Purpose of Establishing a Program of Physical Restoration than in the more sprightly content of the *Journal* as represented by the Anti-Pitressin Factor in the Treatment of Dysmenorrhea, or a discussion of Chronic Relapsing Febrile Nodular Nonsuppurative Panniculitis.

Science is a unit; truth is the same under every garb — and he who advances the one, or defends and demonstrates the other, identifies himself with the only principle that never dies.

Boston M. & S. J., *December 11, 1850*

MASSACHUSETTS MEDICAL SOCIETY

DEATH

Walsh — John E. Walsh, M.D., of Revere, died on November 8. He was in his seventy-eighth year.

Dr. Walsh received his degree from Baltimore Medical College in 1898. He was city physician in Revere.

Two daughters and a sister survive.

NOTES FROM THE MEDICAL EXAMINER*

POST-MORTEM DIAGNOSIS OF DIABETES MELLITUS

Occasionally the medical examiner or the hospital pathologist is required to investigate a case in which the probability of death from diabetic acidosis must be evaluated. Inasmuch as no absolute pathological criteria for the diagnosis of diabetes are available and post-mortem chemistry is subject to somewhat different interpretation than ante-mortem studies, the following items should be considered.

Urine

Starvation as well as diabetes may produce acetone and other ketone bodies in the urine. The finding of large amounts of ketone bodies substantiates acidosis but not necessarily diabetic acidosis. Sugar determinations on post-mortem urine prior to fermentation may be interpreted essentially the same as with ante-mortem urine. The presence of highly positive Benedict tests and large amounts of ketones in urine is probably the best single indication of diabetic acidosis prior to death since urinary sugar is absent in starvation.

Blood

Blood in the right side of the heart and inferior vena cava is subject to tremendous post-mortem rises in glucose content owing to glycogenolysis in the liver with diffusion to the nearby intravascular blood. Thus, sugar concentrations of 600 to 1000 mg. per 100 cc. are of no significance in blood from these sources. Blood in the left side of the heart in the absence of cardiac septal defects is not influenced by liver glycogenolysis, nor is significant sugar produced by post-mortem breakdown of cardiac muscle glycogen.[1] Elevated glucose levels in blood in the left side of the heart must be interpreted cautiously, however, since the release of epinephrine from the adrenal glands in the agonal period of an asphyxial or other slow death may lead to marked liver glycogenolysis with elevations in the systemic blood sugar; thus, in cases of carbon monoxide poisoning and hanging, blood sugar values in the left side of the heart have been in the range of 200 to 600 mg. per 100 cc. in nondiabetic patients.

Glucose disappears from the blood in the post-mortem period at a variable rate affected principally by the rate of cooling of the body. In experimental subjects held at 37°C. an average drop in blood glucose of 13 mg. per 100 cc. per hour was observed. At 27.5°C. the average drop was 6 mg., and at 3°C., 1 mg. per 100 cc. per hour.[1]

Spinal Fluid

The cerebrospinal fluid, although subject to the same agonal rise in dextrose content as the blood, ordinarily shows it to a lesser degree and likewise shows a somewhat slower rate of post-mortem glycolysis. Naumann[2] states that a post-mortem cerebrospinal-fluid glucose of more than 200 mg. per 100 cc. will establish the presence of diabetes, provided pancreatitis is absent and glucose was not given intravenously shortly before death. Further evaluation of his statement is desirable.

The carbon dioxide combining power of blood and spinal fluid is practically useless for determining the presence of ante-mortem acidosis. The blood carbon dioxide combining power may drop to 10 vol. per cent or below within an hour or two of death. Spinal-fluid carbon dioxide combining power is somewhat less labile, but likewise is probably of no value if more than an hour or two has elapsed after death.

Pathological Criteria

Three groups of nonspecific pathological findings occur in diabetes. Each may occur in other diseases, and many persons dead of diabetic acidosis fail to show any of these changes. They are as follows:

Pancreas. Eighty per cent of cases of severe diabetes demonstrate an appreciable degree of pancreatic fibrosis, either interacinar or interlobular, or both. The islands of Langerhans may show hyalinization with destruction of epithelial cells, hydropic degeneration of beta-cell cytoplasm, and fibrosis with more or less complete destruction of the island.

Kidneys. Untreated patients with diabetes in acidosis frequently show severe tubular epithelial damage with glycogen infiltration of the proximal convoluted tubules and Henle's loops. In many cases intercapillary glomerulosclerosis, frequently called the Kimmelstiel–Wilson's lesion, is observed. Acute pyelonephritis with necrotizing papillitis is another lesion occurring particularly in diabetic persons although it is found in other patients in the presence of urinary-tract obstruction.

Liver. The liver may show depletion of glycogen from the cytoplasm of the parenchymal cells with vacuolar enlargement of the nucleus due to glycogen deposition in that site. Hemosiderosis is noted as the primary cause of diabetes in occasional cases, and if the condition is marked it may be accompanied by the cirrhosis characteristic of that disease.

REFERENCES

1. Hill, E. V. Significance of dextrose and nondextrose reducing substances in postmortem blood. *Arch. Path.* **32**:452-473, 1941.
2. Naumann, H. N. Studies on postmortem chemistry. *Am. J. Clin. Path.* **20**:314-324, 1950.

RUSSELL S. FISHER, M.D.
Chief Medical Examiner of the State of Maryland

*Presented by the Department of Legal Medicine, Harvard Medical School.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

CUT IN SEROLOGIC TESTS FOR SYPHILIS

Owing to a cut in the federal appropriation for the current year beginning with December 1, 1950, the Wassermann Laboratory will no longer be able to perform quantitative flocculation(Hinton) and complement-fixation (Wassermann) tests for syphilis on bloods and spinal fluids submitted by physicians. It will also be necessary to eliminate qualitative complement-fixation tests on bloods and spinal fluids.

A new service, which was to be inaugurated this year, was the determination of total proteins on all positive spinal-fluid samples. This new program will be shelved indefinitely.

The Wassermann Laboratory, however, will continue to perform qualitative blood and spinal-fluid Hinton tests. For the present there will be no cut in the volume of these tests, but if there is a further reduction in federal funds services may have to be curtailed still more.

COMMUNICABLE DISEASES IN MASSACHUSETTS FOR OCTOBER, 1950

RÉSUMÉ

DISEASE	OCTOBER 1950	OCTOBER 1949	SEVEN-YEAR MEDIAN
Chancroid	1	0	1*
Chicken pox	399	307	370
Diphtheria	9	12	19
Dog bite	988	866	842
Dysentery, bacillary	15	15	24
German measles	105	39	47
Gonorrhea	260	221	413
Granuloma inguinale	0	0	0*
Lymphogranuloma venereum	0	0	0*
Malaria	1	1	16
Measles	126	107	401
Meningitis, meningococcal	6	4	6
Meningitis, Pfeiffer bacillus	7	1	3
Meningitis, pneumococcal	1	0	2
Meningitis, staphylococcal	0	0	0
Meningitis, streptococcal	0	0	0
Meningitis, undetermined	7	7	4
Mumps	275	209	326
Poliomyelitis	118	239	99
Salmonellosis	3	24	14
Scarlet fever	149	113	273
Syphilis	111	132	380
Tuberculosis, pulmonary	164	134	228
Tuberculosis, other forms	11	6	16
Typhoid fever	1	1	2
Undulant fever	3	3	3
Whooping cough	245	314	321

*Six-year median.

COMMENT

For the month of October, the only diseases appreciably above the seven-year median were German measles and poliomyelitis.

The following diseases were below the seven-year median: diphtheria, gonorrhea, measles, salmonellosis, scarlet fever, syphilis and whooping cough.

The 118 new cases of poliomyelitis reported in Massachusetts during October represented 37 per cent decrease from the 186 cases reported for the preceding month. This was the first month in which a decrease from the preceding month was reported. The figure for this month, although above the seven-year median, was half as large as the corresponding number (239) for October, 1949.

The 9 cases of diphtheria represented the lowest number reported for the month of October in nine years.

The incidence of whooping cough was the lowest in October for the past twenty-five years.

GEOGRAPHICAL DISTRIBUTION OF CERTAIN DISEASES

Diphtheria was reported from: Boston, 2; Cambridge, 6; Somerville, 1; total, 9.

Dysentery, bacillary, was reported from: Boston, 4; Waltham, 1; Worcester, 9; Wrentham, 1; total, 15.

Encephalitis, infectious, was reported from: Agawam, 1; Brookline, 1; Cambridge, 2: Lee, 1; total, 5.

Hepatitis, infectious, was reported from: Boston, 1; Malden, 1; total, 2.

Malaria was reported from: Beverly, 1; total, 1.

Meningitis, meningococcal, was reported from: Boston, 2; Chicopee, 1; Fitchburg, 1; Framingham, 1; Peabody, 1; total, 6.

Meningitis, Pfeiffer bacillus, was reported from: Bellingham, 1; Brockton, 1; Cambridge, 1; Haverhill, 1; Needham, 1; West Springfield, 1; Worcester, 1; total, 7.

Meningitis, pneumococcal, was reported from: Boston, 1; total, 1.

Meningitis, undetermined, was reported from: Dalton, 1; Fall River, 1; Pittsfield, 1; Wellesley, 1; West Boylston, 1; Westport, 1; Worcester, 1; total, 7.

Poliomyelitis was reported from: Abington, 1; Agawam, 1; Amesbury, 1; Arlington, 3; Ayer (Ft. Devens), 1; Barnstable, 1; Beverly, 1; Boston, 6; Braintree, 1; Brockton, 4; Brookline, 1; Canton, 2; Chicopee, 1; Colrain, 1; Danvers, 1; Deerfield, 1; Easton, 1; Fall River, 2; Falmouth (Otis Air Force Base), 1; Fitchburg, 1; Framingham, 2; Great Barrington, 1; Hamilton, 1; Haverhill, 1; Holden, 1; Holyoke, 1; Lee, 1; Lenox, 1; Ludlow, 1; Lunenburg, 1; Lynn, 1; Malden, 1; Maynard, 1; Medford, 2; Nantucket, 1; New Bedford, 1; New Salem, 1; Newton, 2; North Adams, 1; Northampton, 2; Oxford, 1; Pittsfield, 8; Plymouth, 1; Quincy, 5; Randolph, 2; Revere, 2; Rutland, 1; Salisbury, 1; Sheffield, 1; Somerville, 1; Southboro, 1; Southbridge, 1; South Hadley, 1; Spencer, 1; Springfield, 4; Stoughton, 3; Wakefield, 1; Waltham, 1; Wayland, 2; Wellesley, 2; Williamstown, 1; Winchester, 1; Woburn, 3; Worcester, 17; total, 118.

Salmonellosis was reported from: Newton, 1; Stoneham, 1; Worcester, 1; total, 3.

Septic sore throat was reported from: Boston, 6; total, 6.

Tetanus was reported from: Boston, 1; total, 1.

Trichinosis was reported from: Adams, 4; Boston, 1; total, 5.

Typhoid fever was reported from: Boston, 1; total, 1.

Undulant fever was reported from: Hubbardston, 1; Monson, 1; Tewksbury, 1; total, 3.

Weil's disease was reported from: Oxford, 1; total, 1.

CORRESPONDENCE

SAUCE FOR THE GANDER

To the Editor: I have just read your excellent editorial entitled "The Mountain Labors," in the November 9 issue of the *Journal*, on the efforts of organized labor to dictate the relations between the licensed doctor of medicine and his patients.

I wonder what the reaction of labor leaders would be if the American Medical Association or any other organized profession of this country tried to dictate the relations between the workers and their employers. If the American Medical Association and the medical profession is as bad as the labor czars try to make the public believe they are, may one ask if it is any more restrictive or any worse than the labor unions themselves, which can exist only on the basis of preventing a worker from working except by permission of the labor unions? To make this prevention as restrictive as possible, not only do they demand huge membership fees, but also, in case of a strike, they use the coercions of fear and physical violence in the effort to enforce their demands. One could write a book citing instances of high fees, coercions, personal violence, rioting and destruction of property as a means of making their dictation triumphant.

Can the unions cite any instances of physicians pursuing any such undemocratic, un-American, and uncivilized course of action? What a howl of criticism they would pour forth if the American Medical Association tried to prevent physicians who are not members of the Association from practicing medicine! Yet, this is what labor unions are doing every day to outside workers.

It is gratifying to note from the recent election that the voting public is apparently sick and tired of labor leaders' efforts to rule the country. In the state where they made the most vigorous and most slanderous efforts, the political party they support received its worst defeat.

The American people will stand only so much bullying and insult. When they go on the warpath, let the special interests and the profiteers from propaganda watch out.

CHARLES H. KEENE, M.D.
Editor-in-Chief
The Journal of School Health

Buffalo, New York

AMERICAN PHYSICIANS FELLOWSHIP COMMITTEE

To the Editor: A group of American physicians, whose purpose it is to strengthen the relation between Israelian and American medicine and to maintain the dignity and prestige of the physicians in Israel, has been organized. This organization already has nearly 700 members and has been named the American Physicians Fellowship Committee of the Medical Association of Israel.

The Israel Medical Association, which comprises 97 per cent of all the physicians in Israel, is giving strong backing to this organization, whose membership drive is now beginning. Members of the organization automatically become nonresident fellows of the Israel Medical Association and receive the medical quarterly of the Israel Medical Association, *Harefuah*, written in English, as well as an engraved membership diploma and card. The dues are $10 yearly, and applications will be received at 273 Main Street, Nashua, New Hampshire.

Following are the officers of the new organization: president, Morton J. Robbins, M.D., Nashua; honorary president, J. M. Rogoff, M.D., University of Pittsburgh; vice-president, Hyman Morrison, M.D., Boston; treasurer, Leo B. Schwartz, M.D., Bronx.

MANUEL M. GLAZIER, M.D.
National Secretary

Boston, Massachusetts

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Physicians' and Nurses' Concise Medical Encyclopaedia. By William H. Kupper, M.D. 8°, cloth, 450 pp., illustrated. Los Angeles, California: Biblion Press, 1950. $7.50.

This small encyclopedia is arranged alphabetically by subjects. It is more adapted for the use of nurses and students than for physicians.

Thrombosis: In arteriosclerosis of the lower extremities. By Edward A. Edwards, M.D., clinical associate in anatomy, Harvard Medical School, instructor in surgery, Tufts College Medical School, consultant in peripheral vascular disease, Joseph H. Pratt Diagnostic Hospital and Hospital of the Massachusetts Soldiers' Home, and chief of Vascular Clinic, Boston Dispensary. 8°, cloth, 74 pp., with 33 illustrations. Springfield, Illinois: Charles C Thomas, 1950. $2.00. (Publication No. 41, American Lecture Series; a monograph in American lectures in circulation.)

This small monograph is well written and discusses the etiology, pathology, symptomatology, diagnosis and treatment in the first three chapters. The last two chapters are devoted to case reports on spontaneous thrombosis and thrombosis secondary to tissue injury.

The Cytologic Diagnosis of Cancer. By the staff of the Vincent Memorial Laboratory of the Vincent Memorial Hospital, a gynecologic service affiliated with the Massachusetts General Hospital, Boston, and the Department of Gynecology, Harvard Medical School. 8°, cloth, 229 pp., with 153 illustrations. Philadelphia: W. B. Saunders Company, 1950. $6.50.

This volume constitutes an atlas on the subject. The photomicrographs, with illustrative drawings and the color plates, are excellent. Descriptive text accompanies the figures and plates. A comprehensive bibliography concludes the text. There is a good index, and the publishing is excellent. The volume should be in all collections on cancer and gynecology.

Infant Nutrition: Its physiological basis. By F. W. Clements, M.D., D.P.H., D.T.M., senior medical officer, Commonwealth Department of Health, Australia, and chief, nutrition section, World Health Organization, Geneva. 8°, cloth, 246 pp., with 14 illustrations. Baltimore: Williams and Wilkins Company, 1949. $4.50.

This small book on infant nutrition discusses tissue metabolism, fetal nutrition and various aspects on metabolism and nutrition in the infant. It comprises a review of the pertinent literature on the subject. Comprehensive bibliographies are appended to the various chapters. The material is well organized and well printed. The printing was done in Great Britain. The book is recommended as a reference source.

Radiographic Atlas of Skeletal Development of the Hand and Wrist: Based on the Brush Foundation study of human growth and development, initiated by T. Wingate Todd, M.B., Ch.B., F.R.C.S. By William W. Greulich, M.A., Ph.D., professor of anatomy, Stanford University School of Medicine; and S. Idell Pyle, M.S., research associate, Brush Foundation and Department of Anatomy, Western Reserve University School of Medicine. F°, cloth, 190 pp., with illustrations. Stanford, California: Stanford University Press, 1950. $10.00.

This beautiful atlas is divided into four parts: general considerations; male standards; female standards; and maturity indicators of individual bones and epiphyses. In 1929 the Brush Foundation began preliminary studies for a long-term investigation of human growth and development. Professor Todd, in 1937, published his *Atlas of Skeletal Maturation of the Hand*. The x-ray standards in this atlas are based exclusively on the studies of the Foundation. In the previous atlas by Professor Todd, outside sources were utilized in addition to his own observations. The publishing is excellent, and the atlas should be in all anatomic, radiologic and orthopedic collections.

NOTICES

SOUTH END MEDICAL CLUB

A luncheon-meeting of the South End Medical Club will be held at the headquarters of the Boston Tuberculosis Association, 554 Columbus Avenue, Boston, on Tuesday, December 19, at 12 noon. Dr. A. Warren Stearns, professor of sociology, Tufts College, will speak on the subject "Psychiatry and General Practice."

Physicians are cordially invited to attend.

94TH INFANTRY DIVISION LECTURES

The 94th (Bay State) Division is sponsoring a series of monthly lectures by prominent physicians in their respective specialties. The third lecture of the 1950-1951 series will be held in the auditorium of Boston University School of Medicine, 80 East Concord Street, Boston, on Thursday, December 21, at 8 p.m.

Dr. Elvin Semrad, clinical director of the Boston State Hospital and assistant professor of psychiatry at Boston University School of Medicine, will speak on the subject "Psycho-Sexual Development."

All interested physicians, whether reserve officers or not, are cordially invited to attend this carefully planned program. Reserve officers will be given one point credit if authorized by the instructor of their unit of assignment. A psychiatric film will be shown during this period.

(*Notices concluded on page xv*)

NOTICES (*Concluded from page 978*)

THIRTEENTH BRITISH CONGRESS OF OBSTETRICS AND GYNAECOLOGY

The thirteenth British Congress of Obstetrics and Gynaecology will be held at Leeds, Yorkshire, on July 8, 9, 10 and 11, 1952. The subjects for discussion are as follows: abnormal uterine action in labor; stress incontinence of urine. The place of the pediatrician in a maternity unit; and genital tuberculosis in the female.

All communications relating to the Congress should be addressed to the Secretary, B. L. Jeaffreson, M.D., F.R.C.S., F.R.C.O.G., 32 Park Square, Leeds 1, Yorkshire, England.

SOCIETY MEETINGS AND CONFERENCES

DECEMBER 2–23. Springfield Hospital. Page 842, issue of November 23.

DECEMBER 18. Hartford Medical Society. Page 680, issue of October 26.

DECEMBER 18. New England Cardiovascular Society. Page 938, issue of December 7.

DECEMBER 19. South End Medical Club. Page 978.

DECEMBER 20. Greater Boston Medical Society. Page 898, issue of November 30.

DECEMBER 21. 94th Infantry Division Lecture. Page 978.

JANUARY 3. Hampshire District Medical Society. Page 170, issue of July 27.

JANUARY 11. The Diagnosis and Therapy of Lesions Producing Gastrointestinal Hemorrhage. Dr. Claude Welch. Pentucket Association of Physicians. 8:30 p.m. Haverhill.

JANUARY 22. Boston Lying-in Hospital Obstetric Round-Table Conference. Page 629, issue of October 19.

JANUARY 23. Norfolk District Medical Society. Page 629, issue of October 19.

JANUARY 31. American Academy of Orthopaedic Surgery (see Kappa Delta Award for Research in Orthopedic Surgery). Page 736, issue of May 4.

FEBRUARY 13. New England Society of Anesthesiologists. Page 512, issue of September 28.

FEBRUARY 27. Norfolk District Medical Society. Page 629, issue of October 19.

MARCH 26. Boston Lying-in Hospital Obstetric Round-Table Conference. Page 629, issue of October 19.

MARCH 27. Norfolk District Medical Society Page 629, issue of October 19.

APRIL 9–13. American College of Physicians. Page 296, issue of June 15.

APRIL 10. New England Society of Anesthesiologists. Page 512, issue of September 28.

APRIL 24. Norfolk District Medical Society. Page 629, issue of October 19.

MAY 8. New England Society of Anesthesiologists. Page 512, issue of September 28.

MAY 9. Norfolk District Medical Society. Page 629, issue of October 19.

MAY 22–24. Massachusetts Medical Society. Annual Meeting. Hotel Statler, Boston.

MAY 24–26. American Goiter Association. Columbus, Ohio.

OCTOBER 31. New England Obstetrical and Gynecological Society. Hotel Somerset, Boston.

NOVEMBER 10–21. Pan-Pacific Surgical Association. Page 680, issue of October 26.

JULY 8–11, 1952. Thirteenth British Congress of Obstetrics and Gynaecology. Notice above.

DISTRICT MEDICAL SOCIETIES

HAMPSHIRE

JANUARY 3. 4:30 p.m. Veterans Administration Hospital, Northampton.
MARCH 7. 4:30 p.m. Cooley-Dickinson Hospital, Northampton.
MAY 2. 4:30 p.m. Annual Meeting. Jones Library, Amherst.

NORFOLK

JANUARY 23.
FEBRUARY 27.
MARCH 27.
APRIL 24.
MAY 9. Annual Dinner.

All meetings except the Annual Dinner will be held at the Boston Medical Library, 8 Fenway, at 8:00 p.m.

CALENDAR OF BOSTON DISTRICT FOR THE W[illegible] THURSDAY, DECEMBER [illegible]

THURSDAY, DECEMBER 21

*9:00–10:00 a.m. Grand Rounds. Robert Breck[illegible]
*9:00–11:00 a.m. Medical Grand Rounds. Joseph H. [illegible] Hospital.
*8:00 p.m. 94th Infantry Division Lecture. Auditori[illegible] University School of Medicine.

FRIDAY, DECEMBER 22

*9:00–10:00 a.m. Medical Conference. Joseph H. Pratt Diagnostic Hospital.
*9:00 a.m.–12:00 m. Combined Medical and Surgical Staff Rounds. Peter Bent Brigham Hospital.
*10:00 a.m. Surgical Clinic. South End Health Unit, 57 East Concord Street, Boston.
*12:00 m.–1:30 p.m. Surgical Pathological Conference. Joseph H. Pratt Diagnostic Hospital.
*1:30 p.m. Tumor Clinic. Out-Patient Department, Mount Auburn Hospital, Cambridge.
*2:00–4:00 p.m. Therapeutic Conference. Joseph H. Pratt Diagnostic Hospital.
*4:00–6:00 p.m. X-Ray Conference. Joseph H. Pratt Diagnostic Hospital.

SATURDAY, DECEMBER 23

*9:00–10.00 a.m. Surgical Grand Rounds. Joseph H. Pratt Diagnostic Hospital.

TUESDAY, DECEMBER 26

*12:15–1:15 p.m. Clinicoroentgenological Conference. Peter Bent Brigham Hospital.
*1:30–2:30 p.m. Pediatric Rounds. Burnham Memorial Hospital for Children, Massachusetts General Hospital.

WEDNESDAY, DECEMBER 27

*12:00 m. Clinical Discussion. Margaret Jewett Hall, Mount Auburn Hospital, Cambridge.
*12:00 m.–1:00 p.m. Clinicopathological Conference. (Children's Medical Center.) Amphitheater, Peter Bent Brigham Hospital.

*Open to the medical profession.

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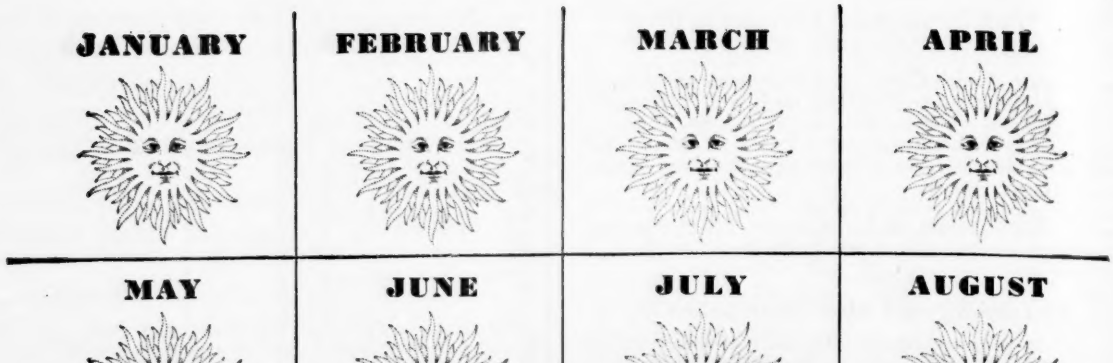

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Mead's Oleum Percomorphum permits a happy independence of the sun as a source of vitamin D. Neither rain nor clouds nor shorter winter days interfere with the child's receiving his daily quota of vitamin D when dependable Mead's Oleum Percomorphum is administered.

Highly potent, Mead's Oleum Percomorphum is economical, too. It provides your patients with year-round protection against deficiency of vitamins A and D

Mead's Oleum Percomorphum is available in liquid form in bottles of 10 and 50 cc., accompanied by a dropper for easy dosage measurement.

Easy-to-take Mead's Oleum Percomorphum Capsules, ideal for older children and adults, are available in bottles of 50 and 250.